Energy & Technology Review

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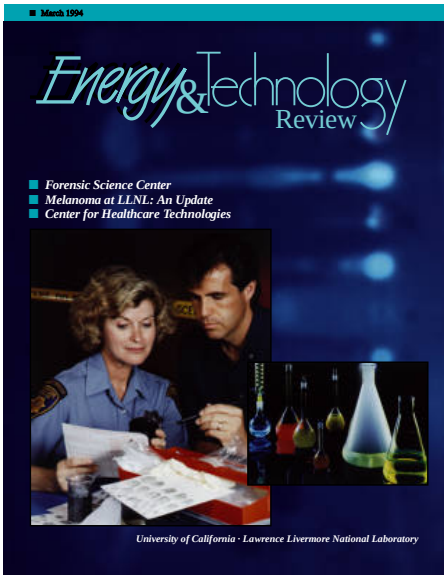
March 1994

Energy & Technology Review

- *Forensic Science Center*
- *Melanoma at LLNL: An Update*
- *Center for Healthcare Technologies*

University of California · Lawrence Livermore National Laboratory



About the Cover

The Laboratory's Forensic Science Center focuses on detecting and analyzing unknown compounds at extremely low levels. Principal materials analyzed to date have included narcotics, explosives, chemical-warfare-related agents, and human remains. In the larger photo, Jeff Haas (right), a chemist from the Center, and Ernie Pelkey, a forensic specialist from the Livermore Police Department, determine the composition of imaging materials used to visualize latent fingerprints on the sticky side of duct tape. The smaller photo shows various fluorescent chemicals that can be visualized at trace levels; they are used for diagnostic purposes in chemical identification. The background image is a fluorescent pattern generated on a thin-layer chromatography plate. Each of the bright spots represents a unique chemical that has been isolated from body fluids. For more information about the analytical capabilities of the Forensic Science Center, see the article on p. 1.

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About the Journal

The Lawrence Livermore National Laboratory, operated by the University of California for the United States Department of Energy, was established in 1952 to do research on nuclear weapons and magnetic fusion energy. Since then, in response to new national needs, we have added other major programs, including technology transfer, laser science (fusion, isotope separation, materials processing), biology and biotechnology, environmental research and remediation, arms control and nonproliferation, advanced defense technology, and applied energy technology. These programs, in turn, require research in basic scientific disciplines, including chemistry and materials science, computing science and technology, engineering, and physics. The Laboratory also carries out a variety of projects for other Federal agencies. *Energy and Technology Review* is published monthly to report on unclassified work in all our programs. Please address any correspondence concerning *Energy and Technology Review* (including name and address changes) to Mail Stop L-3, Lawrence Livermore National Laboratory, P.O. Box 808, Livermore, CA 94551, or telephone us at (510) 422-4859.

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Energy & Technology Review

Forensic Science Center

The Forensic Science Center houses a variety of state-of-the-art analytical tools ranging from gas chromatograph/mass spectrometers to ultratrace DNA detection techniques. The Center's multidisciplinary staff provides expertise in organic and inorganic analytical chemistry, nuclear science, biochemistry, and genetics useful for supporting law enforcement and for verifying compliance with international treaties and agreements.

SINCE 1991, the Laboratory's Forensic Science Center has focused a comprehensive range of analytical expertise on issues related to nonproliferation, counterterrorism, and domestic law enforcement. During this short period, LLNL's singular combination of human and technological resources has made the Center among the best of its kind in the world. The Center has already demonstrated impressive analytical capabilities in organic, inorganic, and biological chemistry as well as in other disciplines.

What is forensic science? Traditionally, the term has been applied to the scientific analysis of evidence in the context of civil or criminal law. More recently, forensic science is increasingly being used to monitor or verify compliance with international treaties and agreements, especially those dealing with weapons of mass destruction. This new concern reflects the substantial changes in the international environment brought about by the end of the Cold War. For example, clandestine attempts by nations to manufacture or acquire weapons of mass destruction have stimulated efforts to develop the most up-to-date technologies to ensure that intelligence information is analyzed as accurately and reliably as possible. International terrorism is another concern. Identifying terrorists by tracing their activities, as in the recent bombing of the World Trade Center in New York City, is a challenge that can require all the resources of forensic science.

The extension of traditional forensic science to these and other areas calls for facilities that are able to support comprehensive, multidisciplinary efforts. It is this challenge that the Laboratory's Forensic Science Center was designed to meet. The Center houses a variety of state-of-the-art analytical tools ranging from gas-chromatograph/mass spectrometers to ultratrace DNA detection techniques. In the hands of an experienced staff of specialists, these and other technologies deliver a full range of forensic science capabilities.

Nuclear Proliferation

As the threat of clandestine nuclear proliferation grows, the task of

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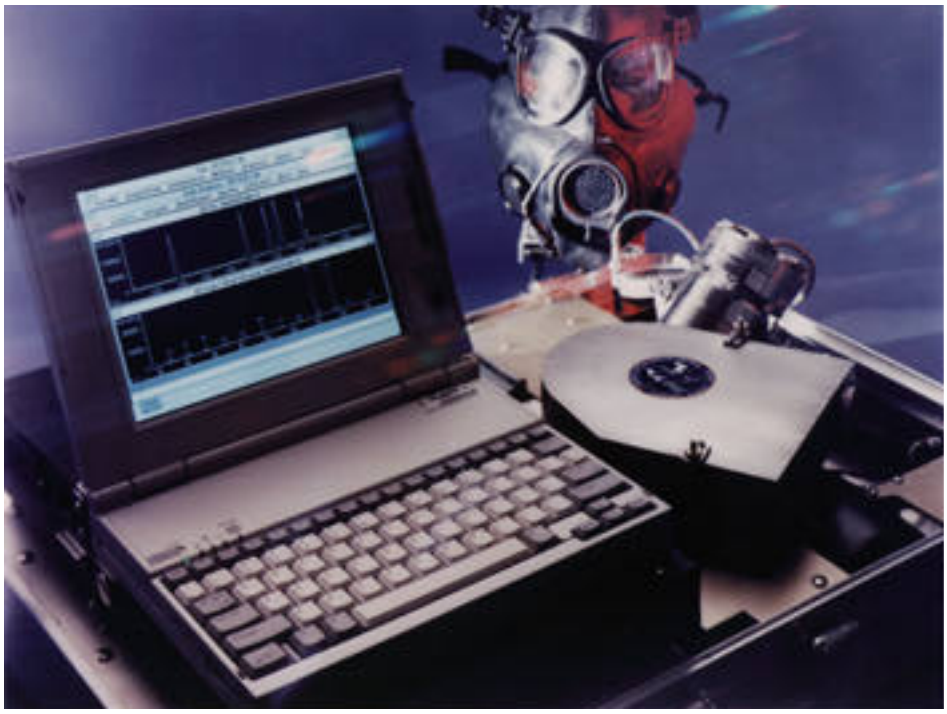

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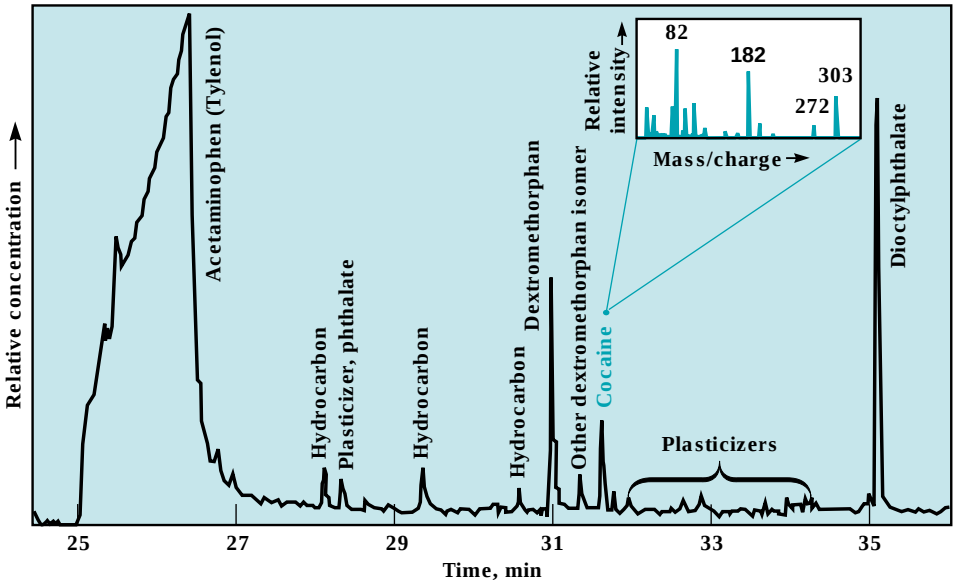

Figure 1. **(a) Our portable gas chromatograph/mass spectrometer (GC/MS) can be used to analyze any liquid, solid, or gas chemical sample in the field. Results from a typical GC/MS analysis (b) show the separation of compounds in the sample. Shown here is a sample of confiscated cocaine, which had been adulterated with Tylenol and other compounds. Identification of the various compounds is achieved through analysis of the ion fragmentation patterns of some 2000 individual mass spectra. The inset graph is one such mass spectral fragmentation pattern, which reveals enough structural information to identify the compound as cocaine.**

acquiring definitive information about a suspect nation's present and future nuclear capabilities becomes more demanding and complex. Such information includes activities related to the processing, procurement, diversion, or dispersion of special nuclear material.

Nuclear-related activities produce a variety of indicators. High-explosive implosion tests, for example, leave tell-tale chemical residues in the environment. The detection of distinctive radionuclides or enriched isotopic species is another sign of a clandestine nuclear program.

To strengthen the Center's analytical capabilities, it has teamed with Laboratory experts in nuclear, radiochemical, isotopic, and inorganic chemistry. This partnership expands the Center's technology base to include many varieties of sensitive equipment for detecting and discriminating all forms of nuclear radiation.

New Approaches to Identifying Chemical Samples

Unknown samples arrive at the Center in many different forms and states of stabilization. Some are water, vegetation, or soil samples; others are "wipes" of substances that may be related to clandestine weapons-production activities. Many such substances are present only in minute quantities whose characteristic chemical "signatures" may be masked by a host of background chemicals also present in the sample. Others have deteriorated into decomposition products. Many are contaminated by extraneous chemicals. To analyze and interpret such samples accurately, we must be able to isolate and identify all their component chemical species as well as their relative concentrations.

Chemical weapons of mass destruction are a focus of monitoring

under the provisions of international treaty, including the Chemical Weapons Convention of 1989. The demands of analyzing unknown chemical samples obtained from a variety of sites around the world have stimulated the development of new technologies. In addition, inspections in support of the Chemical Weapons Convention may not allow suspect samples to be removed to a laboratory; rather, they must be analyzed on-site. We have designed field-analysis kits that can analyze a sample shortly after it is taken, an advantage when dealing with substances that may be unstable, highly reactive, or otherwise perishable.

Remote Chemical Monitoring System

One of these technologies under development is a portable chemistry analyzer known as an ion cyclotron resonance mass spectrometer (ICR-MS). The design of the ICR-MS is based on the principle of the so-called Penning ion trap. Ions of the target compound are injected into a small chamber containing electrodes that generate a static axial electric field. A magnetic field produced by a permanent magnet radially confines the ions within the trap. The high homogeneity of the magnetic field enables us to make extremely accurate mass-spectroscopic measurements.

The ICR-MS can be configured to detect specific chemicals at very low levels of concentration. The low power requirements of the instrument and its simple electronic circuitry, together with the compactness of the spectrometer, the vacuum system, and the computer, permit a very small package. (The ICR-MS has the potential to fit within an enclosure no larger than a coffee can.) We are also working to develop a version that can be left unattended in the field to perform diagnostic chemical analyses.

Chemistry Lab in a Suitcase

Another technology we have developed is a miniature gas chromatograph/mass spectrometer (GC/MS). Completely self-contained in a 28-kg (~61-lb), suitcase-sized package (Figure 1a), this instrument is optimized to detect ultratrace (microgram or less) quantities of narcotics and compounds related to chemical-warfare agents, including their precursors and decomposition products. This instrumentation is ideally suited to support most nonproliferation efforts and investigations related to chemical pollutants released into the environment.

Gas chromatography is a technique widely used to separate mixtures of compounds. In our GC/MS, a solid, liquid, or air sample is injected into the end of a long and very small, hollow quartz column through which hydrogen gas is flowing continually. With heat, the sample is rapidly vaporized into an aerosol and carried into the column, where each component in the mixture is separated. Because chemicals all have different vapor pressures and polarities, each will migrate down the heated, gas-filled column at a different rate. The various chemical species, therefore, are completely separated from the initial mixture and reach the mass spectrometer at different times (typically, over a period of 2 to 45 min) in a relatively pure form.

As each chemical enters the mass spectrometer, it is bombarded with an electron beam, which causes the molecules to break apart into fragment ions. These fragments are sorted and displayed for the operator to study (see Figure 1b). Each chemical produces a unique fingerprint of fragment ions that is used to identify the compound. GC/MS can analyze samples as small as a grain of salt, and total unknowns can be conclusively identified very quickly. The miniature GC/MS is now carried inside a suitcase, and we are working to reduce its size further so that it can fit into a briefcase.

Airborne Mass Spectrometer

A new mass spectrometer that we are currently building and testing allows extremely low levels (a few parts per trillion) of chemicals in air to be collected and detected very rapidly. Having the sensory capability of a German Shepherd guard dog, this mass spectrometer has a combined ion-storage trap and time-of-flight (IT/TOF) configuration (Figure 2a).

The new instrument draws air into an inlet port where any trace chemicals are ionized. The molecular ions are then drawn into an ion-storage trap, where they are contained by radiofrequency-driven electrodes. After a sufficient amount (about 10 pg; 1 pg = 10^{-12}g) of target chemicals have been stored (every 10–100 ms), they are pulsed down a flight tube, detected, and displayed for the operator (see Figure 2b). This new instrument is unique in that it can acquire data on the order of thousands of spectra per second, making it suitable for high-speed aircraft sampling of air samples. Potential applications include identifying hazardous and chemical spills, monitoring industrial stacks and materials for volatile compounds, detecting concealed contraband, and surveying the environment. This instrument is particularly useful for sampling a released plume of smoke or airborne chemical that is only available for an instant in time.

We have completed a laboratory-size IT/TOF instrument (Figure 3). Work is now in progress to design and build a smaller transportable instrument that can be placed under the wing of a surveillance aircraft.

Detecting Low Levels of Chemiluminescent Compounds

Researchers, intelligence agencies, and environmental scientists must sometimes identify minute quantities of compounds that emit light when exposed to certain chemicals. We are using a technique called high-performance liquid chromatography to probe the lower limits of detection for a family of such compounds, called polycyclic aromatic hydrocarbons.

Liquid chromatographic instruments mix the substance to be analyzed with hydrogen peroxide (H_2O_2) and another activating chemical, bis(2-4,6-trichlorophenyl) oxalate (TCPO). The target compound emits light of a characteristic frequency—a phenomenon known as chemiluminescence—that can be recorded and used to identify it at extremely low levels. Such compounds also give off light when illuminated with certain short frequencies of light, a process known as fluorescence.

We use liquid chromatography with tandem ultraviolet absorption, fluorescence, and chemiluminescence detectors and compare the results of the three techniques for different concentrations of a target compound. Our goal is to determine the relative sensitivities of the three detection methods for extremely small (nanogram to picogram) concentrations of compounds against backgrounds that may include a variety of contaminants.

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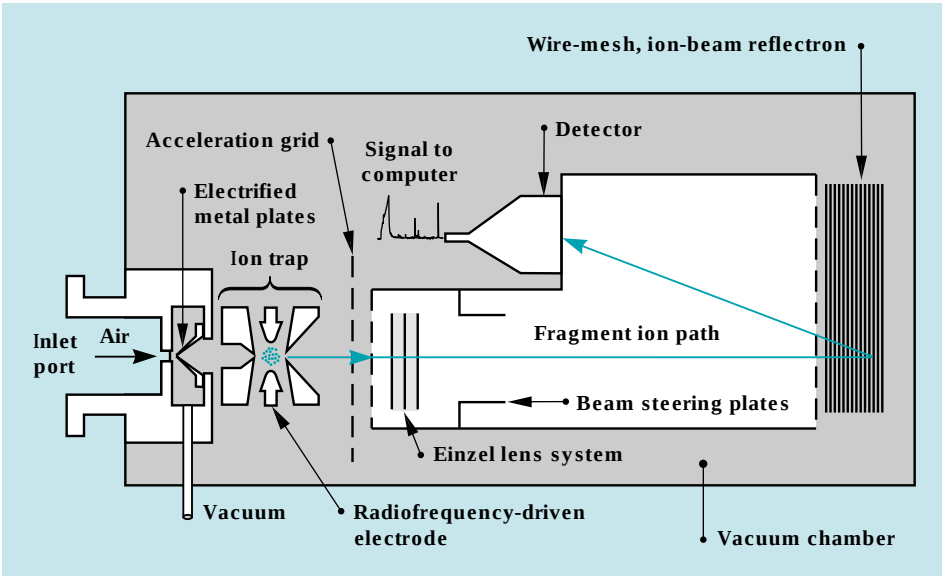

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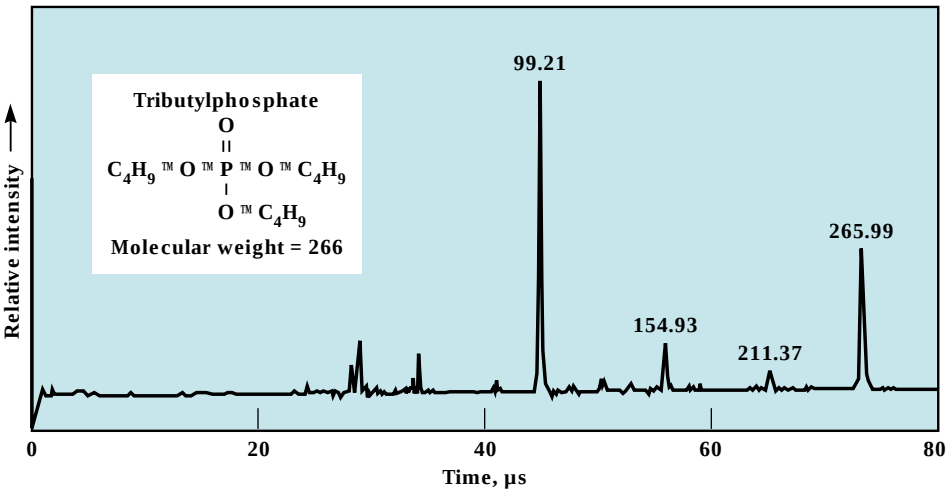


Figure 2. The ion-storage trap/time-of-flight (IT/TOF) mass spectrometer can detect and analyze trace chemicals in any air sample. The instrument (a) is divided into three regions: an ionization source, an ion-storage trap, and a mass spectrometer. The mass spectrometer separates the ions according to their mass, which usually takes 10–100 µs. Shown in (b) is an ion fragmentation pattern that reveals predominant mass-to-charge ratios of 99.21, 154.93, 211.37, and 265.99. These species are consistent with the presence of tributylphosphate, a chemical indicative of uranium reprocessing for the recovery of plutonium.

An International Effort

Activities in support of the Chemical Weapons Convention and the Nuclear Non-Proliferation Treaty are international in scope. In cooperation with about a dozen other countries, the Forensic Science Center is participating in a series of "round-robin" exercises designed to probe the capabilities of analytical chemistry facilities around the world. In these continuing exercises, realistic samples of a variety of substances, whose identities are known only to the preparing agency, are sent out to the participants, who analyze them and report their results. Target compounds

are often present at extremely low concentrations.

Seventeen laboratories in fourteen countries participated in Round Robin III (1992). A laboratory in The Netherlands prepared the samples, which consisted of concrete, paint, and rubber matrices spiked with chemical-warfare-related compounds (e.g., precursors and degradation products). Among the analytical methods used by participating laboratories were GC/MS, Fourier-transform infrared spectrometry, and nuclear magnetic-resonance spectrometry.

The Laboratory's Forensic Science Center did very well in the exercise, one of the few facilities to do so. Participation in these round-robin exercises has deepened our understanding of the operational parameters needed to detect key chemical signatures in "real-world" environmental samples.

Domestic Activities

Not all of the Forensic Science Center's activities are in support of international investigations. We have performed some domestic investigations to learn more about the value of our technologies and to gain practical experience with real-world samples. We have had excellent success in applying our resources to cases involving extraordinary circumstances or demanding unusually high-quality forensic analyses. Some of these studies have been undertaken at the request of local regulatory or law-enforcement agencies.

What Ever Happened to Baby Jane?

One such recent case began in October 1988, when a shallow, unmarked grave in a remote area of northern California yielded the decomposed body of a woman. A lengthy search of dental records identified her to be a Berkeley artist reported missing two years earlier, together with her 18-month-old baby. A detective's hunch led the police to suspect a link between the case and the body of an infant that had washed ashore in Tiberon several months before the woman's body was found. The media dubbed the unidentified infant "Baby Jane Doe." To establish whether the two were related, in the summer of 1992, the Forensic Science Center was requested to do supporting

Figure 3. Our laboratory-size ion-storage trap/time-of-flight (IT/TOF) instrument. We are currently designing a smaller transportable instrument.

Figure 4. To determine whether an unidentified baby and woman were related, the Center was called upon to analyze cell samples from both bodies. Using the polymerase chain reaction, LLNL researchers replicated the gene samples. Here, biomedical scientist Marge Segraves is loading a gene segment suspended in a gel before the samples are separated for comparison.

DNA analyses of cell samples from both bodies (Figure 4).

DNA analysis requires only a few intact body cells, which can be taken from minute traces of blood or tissue. In this case, the analysis was complicated by the fact that both bodies were badly decomposed. Researchers used a technique called the polymerase chain reaction (see the box on p. 7) to amplify and then compare the DNA samples. The same DNA segment taken from different individuals can be of different lengths. The more closely two individuals are related, the more likely are their genes to match in length. After using the polymerase chain reaction to amplify the DNA samples, the replicated segments are suspended in a gel. An electric current applied to the gel then separates the DNA fragments by size for comparison.

Although not conclusive, our analysis suggested it was highly likely that the woman was the mother of Baby Jane. An eerie aspect of the case was that the infant appeared to be about the same age as when it had disappeared two years earlier. This circumstance led authorities to conclude that both bodies had been frozen for some time before being disposed. The woman's husband was sought as the prime suspect in the killings. Although he never confessed, he committed suicide in 1992, leaving a note in which he asked for forgiveness. The case was subsequently closed by the Marin County District Attorney's Office.

Cold Fusion Heats Up

In another case, we were asked by California's Occupational Safety and Health Administration (OSHA) to analyze debris from an explosion that occurred during a 1992 "cold-fusion" experiment at a research laboratory in California (Figure 5). Such experiments began in 1989, when two University of Utah scientists conducting electrochemistry experiments reported the production of excess heat that they attributed to hitherto unknown thermonuclear fusion processes. For a brief time, the cold-fusion phenomenon captured public attention as a new and possibly revolutionary energy source. Since then, however, the majority of the scientific community has rejected these claims, attributing positive experimental results to various sources of error.

In the explosion, one researcher was killed and several others were injured. Drawing upon the Laboratory's scientific expertise in many different fields—about 65 professionals in all—we performed an extensive suite of analytical tests on the debris. We eliminated any nuclear reactions, high explosives, or illegal tampering as possible causes of the explosion. An unanticipated result of our investigation was that machine-shop lubricating oil could have been a potential contributor to the incident,

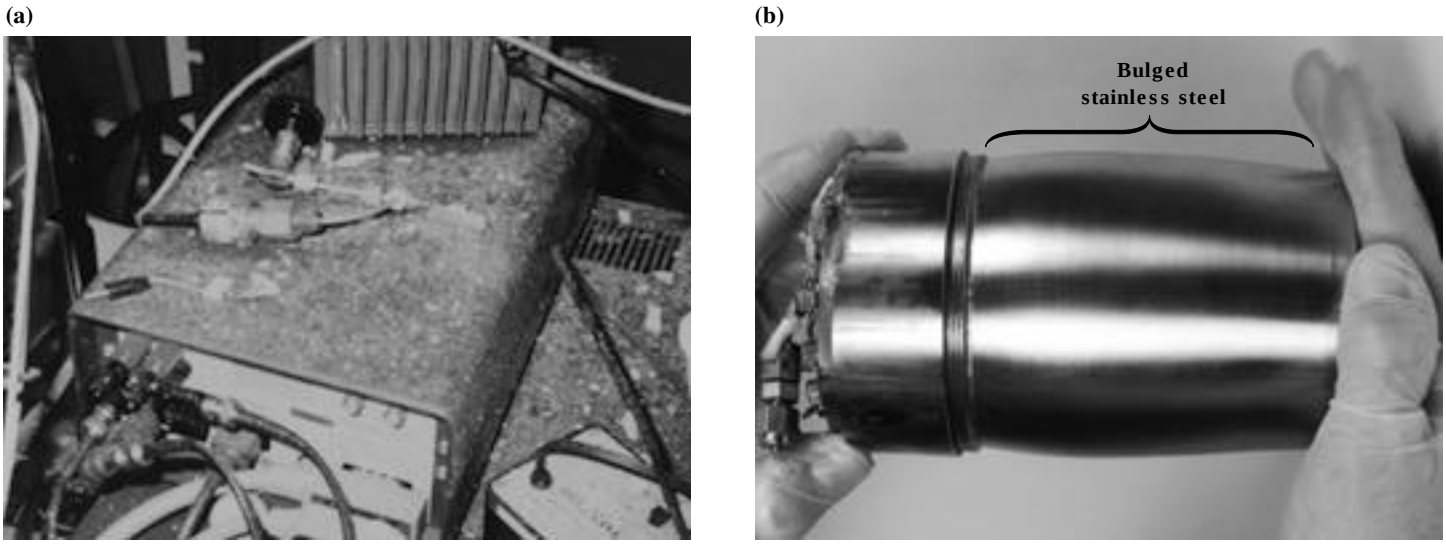
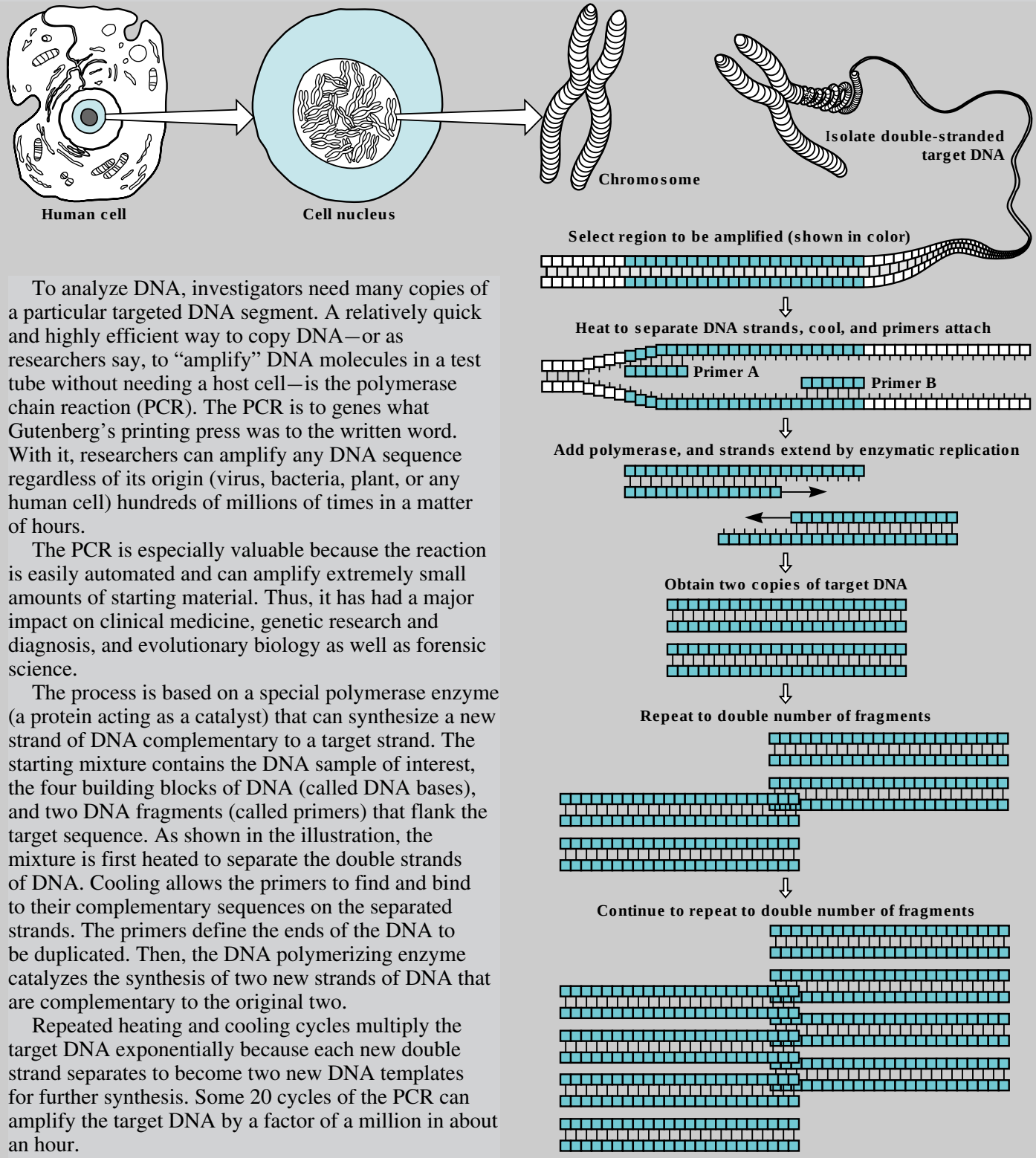


Figure 5. In 1992, an explosion occurred during a "cold-fusion" experiment at a research laboratory in California. About 65 LLNL scientists were called upon to analyze the debris (a) to shed light on potential causes of the explosion. The distended cold-fusion cell after the explosion is shown in (b). Our most unanticipated result was that machine-shop lubricating oil could have been a potential contributor to the incident.[1]

The Polymerase Chain Reaction: A Printing Press for DNA



To analyze DNA, investigators need many copies of a particular targeted DNA segment. A relatively quick and highly efficient way to copy DNA—or as researchers say, to "amplify" DNA molecules in a test tube without needing a host cell—is the polymerase chain reaction (PCR). The PCR is to genes what Gutenberg's printing press was to the written word. With it, researchers can amplify any DNA sequence regardless of its origin (virus, bacteria, plant, or any human cell) hundreds of millions of times in a matter of hours.

The PCR is especially valuable because the reaction is easily automated and can amplify extremely small amounts of starting material. Thus, it has had a major impact on clinical medicine, genetic research and diagnosis, and evolutionary biology as well as forensic science.

The process is based on a special polymerase enzyme (a protein acting as a catalyst) that can synthesize a new strand of DNA complementary to a target strand. The starting mixture contains the DNA sample of interest, the four building blocks of DNA (called DNA bases), and two DNA fragments (called primers) that flank the target sequence. As shown in the illustration, the mixture is first heated to separate the double strands of DNA. Cooling allows the primers to find and bind to their complementary sequences on the separated strands. The primers define the ends of the DNA to be duplicated. Then, the DNA polymerizing enzyme catalyzes the synthesis of two new strands of DNA that are complementary to the original two.

Repeated heating and cooling cycles multiply the target DNA exponentially because each new double strand separates to become two new DNA templates for further synthesis. Some 20 cycles of the PCR can amplify the target DNA by a factor of a million in about an hour.

and we recommended to OSHA that all cold-fusion containers should be scrupulously cleaned in the future. We have submitted a paper describing the most important of these results to a peer-reviewed journal.[1]

The Japanese Connection

During a San Francisco conference last year, a Japanese criminologist described new imaging materials that could have important applications in fighting international and domestic crime. The materials enable investigators to visualize latent fingerprints on the gummed surface of duct tape, often used in bombings and kidnappings. The Japanese demonstrated a black powder that—when mixed with a liquid, applied to the desired surface, and then rinsed off—leaves a small residue that highlights any latent fingerprints.

Although American law enforcement officials showed considerable interest in the materials, there was a problem. According to U.S. law, any such material must be accompanied by a Material Safety Data Sheet, which was lacking in this case. Language barriers and differing safety regulations prevented the U.S. from learning the composition directly. A forensic specialist at the Livermore Police Department contacted the Laboratory, and the Forensic Science Center agreed to analyze the materials (Figure 6).

The liquid turned out to be 90% water and 10% propylene glycol, with a trace of detergent. Scanning electron microscopy established that the extremely fine black powder was alumina coated with iron, similar to that used in toners for copying machines or printers.

Last spring, the Center received a letter from the California Criminalistics Institute describing the language and legal difficulties that had earlier frustrated the preparation of a Material Safety Data Sheet. The letter thanked the Laboratory for its analyses, which had provided the necessary information, and announced that the Japanese materials would "soon be made available to forensic print specialists throughout the country."

Figure 6. The Forensic Science Center analyzed and determined the composition of new fingerprint imaging materials from Japan. These materials now allow investigators nationwide to visualize latent prints from previously intractable surfaces, such as the sticky side of adhesive tape.

Summary

Using the comprehensive array of sophisticated technologies from across the entire Laboratory, our Forensic Science Center is able to quickly characterize evidentiary materials of importance both to national security and to forensic aspects of domestic law enforcement. The Center's analytical capabilities feature state-of-the-art sensitivities for detecting virtually any target compound contained in any sample. Our approach maximizes the information returned from limited samples collected by a variety of verification, inspection, monitoring, and law-enforcement agencies. As the pertinent technologies develop, we will continue to enhance these analytical tools.

Key Words: Chemical Weapons Convention; cold fusion; fingerprint imaging materials; Forensic Science Center; Fourier-transform infrared spectrometry; fragmentation ions; gas chromatograph/mass spectrometry (GC/MS); high-performance liquid chromatograph; ion cyclotron resonance/mass spectrometry (ICR/MS); ion storage trap/time-of-flight (IT/TOF); Non-Proliferation Treaty; nuclear magnetic resonance; polymerase chain reaction (PCR); Round Robin III.

Reference

1. P. M. Grant, R. E. Whipple, A. Alcaraz, J. S. Haas, and B. D. Andresen, "Hydrocarbon Oil Found in the Interior of a 'Cold Fusion' Electrolysis Cell After Fatal Explosion," *Fusion Technology* **25**(2), (1994).

For further information contact Brian D. Andresen (510) 422-0903 or Patrick M. Grant (510) 423-6772.

Melanoma at LLNL: An Update

In recent years, the rate of diagnosis of the more lethal form of melanoma among LLNL workers, which was previously elevated, has returned to that of the surrounding geographical area where most employees live. If our program of employee awareness about melanoma, enhanced surveillance, and early diagnosis continues to lead to decreased mortality from this disease, then such an approach may have important public health implications for the broader community.

FROM 1972 to 1977, the Laboratory experienced a diagnosis rate of malignant melanoma among its employees that was three to four times higher than expected based on rates for the surrounding Alameda and Contra Costa counties in the Bay Area.[1] In 1984, Austin and Reynolds from the California Department of Health Services reported the results of their study comparing individuals diagnosed with melanoma and otherwise healthy controls from the Laboratory. These researchers concluded that five occupational factors were "causally associated" with melanoma risk at LLNL.[2] The factors were exposure to radioactive materials, exposure to volatile photographic chemicals, work at Site 300, visits to the Pacific Test Site, and duties as a chemist.

Later external reviews of the report were conducted by experts in epidemiology and biostatistics at the University of North Carolina. These reviewers concluded that the methods Austin and Reynolds had used were appropriate and correctly carried out. However, the conclusion concerning a causal relation between occupational factors and melanoma among employees was overstated, according to the panel of reviewers.

This article summarizes the main results of studies carried out since 1980 and the recent outcome of an extensive, new investigation of the

Moles and Malignant Melanomas

Normal moles, also called nevi, are evenly colored tan or brown spots on the skin that can be flat or raised, as shown in the top two photographs. They are generally round or oval with sharply defined borders. Nearly everyone has such moles, and the overwhelming majority are harmless and do not become malignant.

People with numerous moles or certain unusual moles, called dysplastic nevi, are more likely to develop melanoma. Dysplastic moles are often a mixture of colors and have irregular borders that fade into the surrounding skin. Such moles can be smooth, scaly, or rough and are generally larger than 5 mm in diameter (about the size of a pencil eraser).

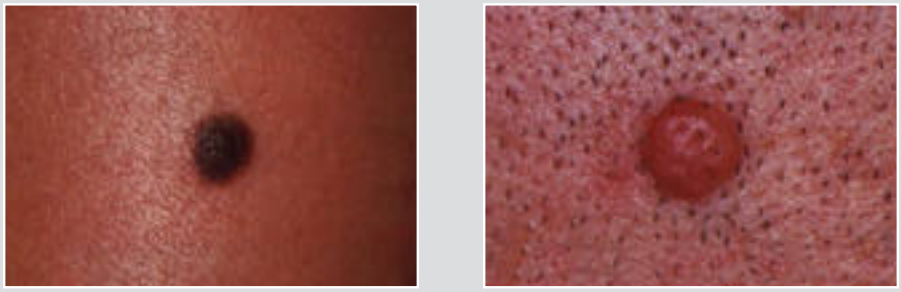
Warning signs suggesting the possible development of melanoma in any mole include oozing, bleeding, alterations in the surface of the mole, and changes in sensation, including itchiness, tenderness, or pain.

Malignant melanoma is characterized by the mnemonic ABCD, where A = asymmetry, B = border irregularity, C = color variation, and D = diameter generally greater than 5 mm.

The initial diagnosis of dysplastic nevi is made during a physical examination by a physician. If a physician suspects melanoma, the diagnosis must be confirmed by first removing one or more suspect moles. This simple procedure, called a biopsy, is performed in 15 to 30 min in a doctor's office or at the Laboratory's Mole Patrol clinic. The biopsy sample is sent to a pathology laboratory for study under a microscope.

Early melanoma can be treated by simple surgical removal of the malignant cells and has very low mortality. Later stages may require more extensive treatment and are associated with higher mortality—thus the importance of early diagnosis and treatment.

Normal moles



(Not to scale) 4 mm

Dysplastic nevi

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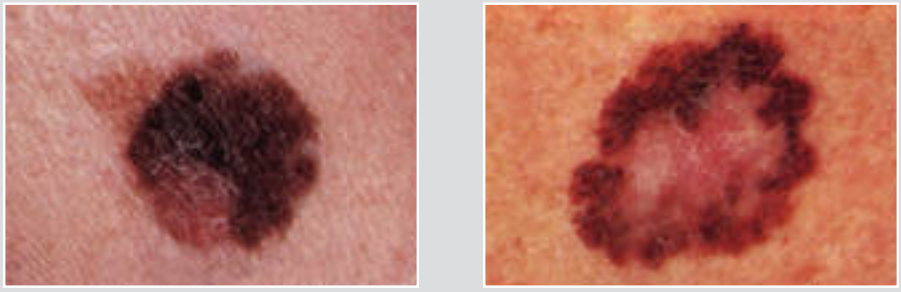
Malignant melanomas



14 mm 28 mm

five occupational factors that were linked by Austin and Reynolds to melanoma cases at the Laboratory. We also summarize our decade-long efforts related to increased awareness about melanoma, skin monitoring, and the possible public health implications of such a program were it applied to the broader community.

About Melanoma

Malignant melanoma is a form of cancer that affects the skin cells (melanocytes) that produce melanin. Melanin is a pigment that protects the skin from damage caused by ultraviolet radiation from the sun. After skin cells are injured by sunlight, melanin production temporarily increases, resulting in a sun tan. Melanoma occurs when melanocytes are transformed into cancer cells that grow uncontrollably. These cancers generally appear in shades of tan, brown, and black on the skin. The box on p. 10 describes normal moles and melanoma in more detail.

Unlike other forms of skin cancer, melanoma may spread rapidly to other parts of the body. When colonies of these malignant cells reach vital organs, they become difficult to treat and are potentially lethal.

A few terms are necessary to understand how melanoma is investigated and reported. Melanoma is characterized by different types of spots or "lesions" found on the skin. Atypical melanocytic hyperplasia (AMH) is thought to be a precursor lesion to melanoma. Noninvasive lesions, called *in situ* lesions, are skin structures associated with early forms of the disease. Such lesions are relatively smaller and less life-threatening than those associated with later forms of melanoma. Invasive lesions have metastatic potential, meaning that they may spread to other parts of the body. Thinner invasive lesions (<0.78 mm thick) are generally less lethal than thicker invasive lesions (>1.5 mm).

Scientists have long known that melanoma is linked to moles. Another known risk factor is excessive sun exposure, especially before age 15 in people with fair skin. Individuals who are from families with multiple cases of melanoma have an additional risk of developing this disease. Because no one is immune to melanoma, early diagnosis is the best defense against mortality from this disease.

Spot Check Program Addresses an Important Public Health Issue

The Laboratory began an educational campaign on melanoma in March 1984. The entire effort, called Spot Check, encourages all employees to examine their moles, record information on the number, size, and location of each one, and report their findings to Health Services personnel. For the last 10 years, all new employees have been given a brochure explaining the relation between melanoma and moles and asked to fill out and return the accompanying Spot Check form.

Dr. Jeffrey Schneider, a dermatologist, has been at the on-site clinic since it was established in July 1984. He now comes to the Laboratory weekly to examine employees and to surgically remove suspicious lesions. Each biopsy specimen is sent to a dermopathologist at the University of California at San Francisco's Melanoma Clinic for review.

As of December 16, 1993, a total of 4851 employees have received one or more skin examinations at the on-site clinic. The results of all examinations and biopsies are stored in a readily accessible computer database. This information places LLNL in a unique position to study the effects of an intensive educational and awareness campaign on the rates of occurrence for various early stages of melanoma.

In October 1993, Dr. Schneider received a grant from the Kaiser Foundation to continue studying melanoma incidence and mortality among Laboratory employees. Over the long term, the data he and others have accumulated can help answer the important question of whether mortality from this disease can be reduced or even eliminated through an effective education program and screening process.

If we do not experience further mortality from melanoma during the next three years, it would be reasonable to conclude that a program and clinic like ours significantly reduces mortality, at least in an educated population such as that at LLNL. Given the worldwide increase in the incidence of melanoma, the possibility of reducing the number of deaths through intensive education and follow-up examinations is an important public health issue.

Worldwide and LLNL Incidence of Melanoma

The incidence of melanoma worldwide has been doubling every decade for the past 30 years. In the U.S., the incidence of this disease is increasing more rapidly than any other cancer among Caucasian men. In Caucasian women, the rate of increase is second to that of lung cancer.

For 1993, the estimated incidence of melanoma in the U.S. was 32,000 invasive cases (about 2.7% of the total cancer incidence) and 6000 noninvasive (*in situ*) cases. In the San Francisco–Oakland metropolitan area, the incidence rate for Caucasians exceeds the national rate by about 25%. The cause of this higher regional rate is not understood, but it may reflect lifestyles associated with greater affluence (and more leisure time) or with increased diagnosis as a result of greater access to physicians by Bay Area residents.

Mortality in 1993 was estimated to be 6800, and men with melanoma died at a substantially higher rate than women. Assuming that there are no future environmental or lifestyle changes, the trends we see indicate that the mortality rate associated with melanoma will begin to decline in a decade or so. (A decline in mortality could result from decreased exposure to sunlight by a better-informed public, increased use of sunscreens by younger people, and increased detection of early lesions by physicians.) Ozone depletion and education of the public about melanoma prevention could influence this prediction in opposite directions. See the box on p. 11 for further discussion of how melanoma education and enhanced surveillance may lead to the prevention of life-threatening forms of melanoma.

At LLNL, the first case of cutaneous (skin) melanoma occurred in 1960, as shown in Figure 1. One case per year was reported in 1963, 1964, and 1968–1970. Then in 1972, a cluster of four cases occurred. During this period, when melanoma incidence was initially rising above the community rate, there were approximately 5000 employees at the Laboratory. The workforce gradually expanded to nearly 9000 before declining within the last few years. Scientists, engineers, and technicians are the most numerous job categories, but all types of administrative and support personnel are represented in the LLNL population.

By 1976, the total number of cases of cutaneous melanoma at the Laboratory was 21; however, only 15 of these cases were known to LLNL's medical department at the time.

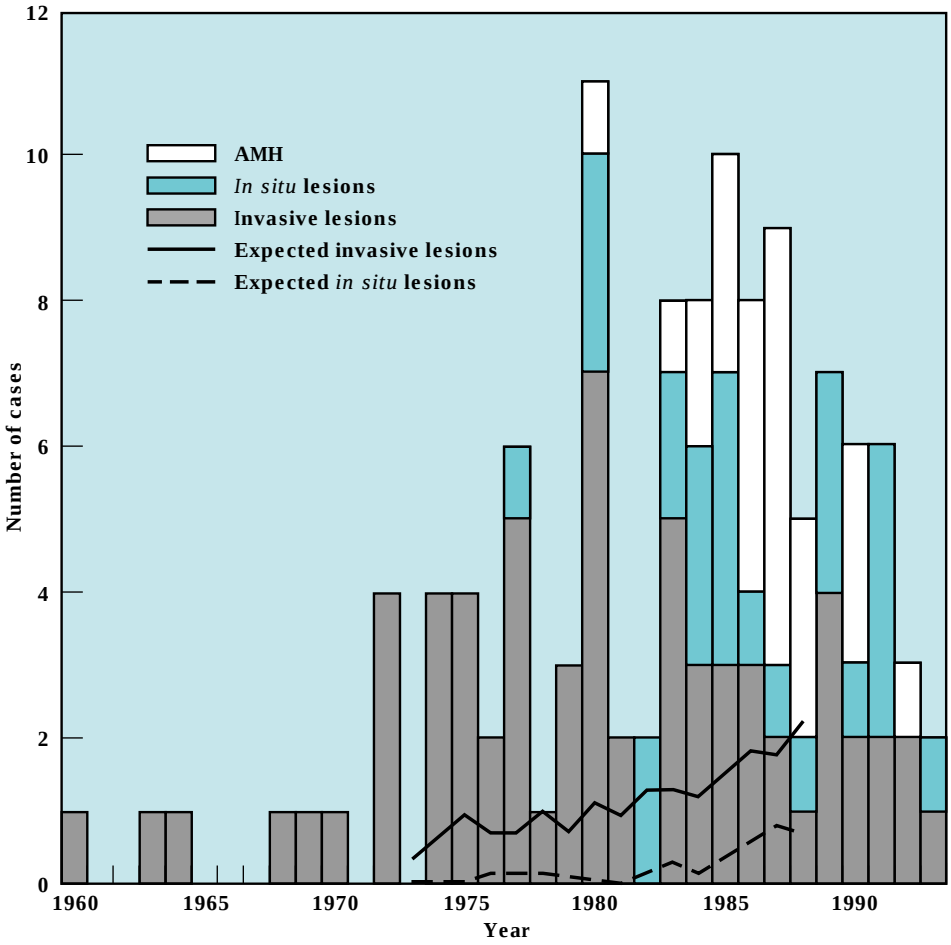


Figure 1. **Number of cases of malignant melanoma among LLNL workers from 1960 to the present. Cases are broken down into three types: atypical melanocytic hyperplasia (AMH), which is thought to be a precursor lesion to melanoma, noninvasive (*in situ*) lesions associated with early forms of the disease, and invasive lesions that have metastatic potential. The cluster of cases in 1972–1977 is what first drew the attention of the Laboratory's medical department.**

(Some people sought diagnosis and treatment from personal physicians and did not always inform Laboratory medical personnel.) LLNL Medical Director Dr. Max Biggs and several physicians in the area became concerned.

In early 1977, with funding from the Laboratory, Dr. Biggs requested assistance from the Resource for Cancer Epidemiology (RCE) of the California Department of Health Services, which maintains the Tumor Registry for the San Francisco Bay Area. Drs. Austin and Reynolds, investigators for the RCE, compared the number of melanoma cases observed among LLNL employees during 1972–1977 with the number expected based on rates for the two adjacent counties where most LLNL employees lived.

The results were released in April 1980.[1] The melanoma incidence rate of 19 known cases in Laboratory employees during the study period was determined to be three to four times greater than that expected. The media publicity generated by this report may have contributed to the spike of 11 new cases in 1980. Retrospective analysis of the data showed that the LLNL incidence rate began to exceed that of the adjacent counties in 1972.

Summary of Studies on Melanoma at LLNL

After receiving the Austin–Reynolds report, LLNL promptly formed a Melanoma Task Group to investigate the problem and monitor research. Members of this Task Group, chaired by Lowry Dobson, were all from the Laboratory. From 1980 to the present, many studies and reviews have been done to understand the nature and possible causes of the increased incidence of melanoma at LLNL. Table 1 summarizes these investigations and their principal conclusions.

DOE Advisory Board

In April 1980, the Secretary of Energy formed an *ad hoc* Advisory Board to review the LLNL data and to identify potential causal factors. The Advisory Board concluded that the melanoma incidence rate among employees did, in fact, exceed the rate in the local community. Although their review did not implicate any specific cause, the Advisory Board noted that "the possibility cannot be excluded that the excess may ultimately prove to reflect the influence of socio-economic factors and lifestyle, rather than exposure to a cancer-causing agent in the workplace."

Second Austin Report

Further DOE-funded studies by Dr. Austin's group found that cancer in general (all types except melanoma) from 1969–1980 was not elevated in LLNL employees above rates in the Bay Area population.[3] Shortly thereafter, Austin and Reynolds identified two factors that might serve as clinical markers of individuals at high risk for malignant melanoma of the skin: parental history of nonmelanoma skin cancer, and the presence of many large moles (5 mm or more in diameter). Whereas genetic factors had been implicated earlier, Austin and Reynolds were the first to identify large moles as a clinical marker for melanoma. These findings have since been confirmed in the epidemiological literature.

Kaiser Foundation Report

In February 1984, a report from the Kaiser Foundation Health Plan of Northern California confirmed the approximately three-times higher incidence of melanoma in Laboratory employees than in non-LLNL Kaiser Plan members residing in the area. The study included 148 Laboratory employees and 216 non-LLNL members. Laboratory employees who were Kaiser Plan members were found to have their skin biopsied for pigmented lesions significantly more often than non-LLNL members. This finding was tentatively ascribed to the awareness of the increased incidence at the Laboratory by employee members and by LLNL and Kaiser Plan medical staff.

Third Austin Report

Then in July 1984, Austin and Reynolds published the results of a study comparing 31 LLNL melanoma cases and 110 matched controls who were interviewed in 1981.[2] Detailed comparisons were made of 180 factors together with statistical analyses of those factors thought to be relevant in possibly causing melanoma. (This study did not require that the controls be employed at the Laboratory for as long as the 31 individuals with melanoma. In addition, the study did not match individuals in the two groups for years of education. The possible significance of this approach will be discussed later in more detail.)

Five occupational factors were asserted to explain the three- to fourfold increase in melanoma incidence. The suggested factors were:

- Exposure to radioactive materials.
- One or more visits to Site 300.
- Exposure to volatile photographic chemicals.
- Visits to the Pacific Test Site during a nuclear test.
- Duties as a chemist.

In this case–control study, it is noteworthy that working at the Nevada Test Site was included as one

Table 1. Timeline and main conclusions of studies on melanoma at LLNL.

Date	Study	Conclusions
1980	Austin report #1	The incidence of melanoma among LLNL employees exceeds the rate in the local community.
1982	Austin report #2	Cancer in general (all types except melanoma) was not elevated in LLNL employees above rates in the Bay Area population from 1969 to 1980.
1984	Kaiser Foundation report	The incidence of melanoma in LLNL employees is about three times higher than in non-LLNL Kaiser Plan members residing in the area.
1984	Austin report #3	Five occupational factors are asserted to explain the three- to four-times higher incidence of melanoma at LLNL: 1. Exposure to radioactive materials 2. Visits to Site 300 3. Exposure to volatile photographic chemicals 4. Visits to the Pacific Test Site during a nuclear test 5. Duties as a chemist
1985	External review	A panel assembled by the University of North Carolina School of Public Health concludes that the design and statistical methods used in the 1984 Austin study were appropriate and properly applied, but conclusions about the causal effect of five occupational factors were overstated.
1987	Further external review	Statistical researchers at the Univeristy of North Carolina further validate the database and models used by Austin but conclude that Austin and Reynolds “overinterpreted” their study. However, three occupational factors remain robust and significant: 1. Working around radioactive materials 2. Working at Site 300 3. Working around volatile photographic chemicals
1991	Kaiser Foundation study on lesion thickness	LLNL employees with melanoma had thinner lesions than non-LLNL Plan members prior to 1976; no difference in lesion thickness is seen after 1976.
1991	LLNL studies on lesion thickness	An independent study of lesion thickness supports thinner lesions among LLNL employees and the possibility that increased surveillance could have contributed to the elevated melanoma rate at LLNL.
1992	Further studies on lesion thickness	Studies at the Stanford University Medical School and at the Northern California Cancer Center conclude that LLNL individuals had thinner lesions than people in the adjacent community during 1974–1985. Increased surveillance could have contributed to the higher rate.
1994	New LLNL study on melanoma among LLNL employees	No occupational factor in the workplace is implicated in the incidence of melanoma at LLNL. Personal and familial characteristics of LLNL melanoma cases resemble those found in other populations.

of the 180 possible occupational risk factors; however, the risk for melanoma among Laboratory people was not significantly increased by one or more visits to that site.

External Review

Because of his expertise in occupational epidemiology, the Laboratory requested Dr. Carl Shy of the Department of Epidemiology at the University of North Carolina to review the Austin–Reynolds data. He assembled a panel of melanoma experts from around the world to critically evaluate the Austin–Reynolds case–control study. This panel was concerned with several questions. Was the Austin–Reynolds study designed properly, and were their statistical methods appropriate? Were the conclusions set forth plausible and reasonable? This panel presented its findings to Laboratory employees in January 1986. In summary, their review found that:

- The design and statistical methods used in the 1984 Austin study were appropriate and properly applied.
- The small number of cases (31) made it very difficult to identify the independent effects of occupational and nonoccupational risk factors.
- The Austin report overstated conclusions about the five occupational factors primarily because experimental evidence linking melanoma causation with these occupational factors was very weak or nonexistent. For example, no other study has found that exposure to radioactive materials leads to melanoma.
- A causal relation between occupational exposures at the Laboratory and the risk of developing malignant melanoma had not been clearly established.
- Some or all of the excess cases could be explained by intense surveillance of moles and a high rate of biopsy. Simply put, the concern among LLNL employees and their physicians about melanoma had increased above that prevalent in the community.

Further North Carolina Reviews

At the same time that Dr. Shy's panel was conducting its review, we asked Dr. Lawrence Kupper—a nationally recognized expert in biostatistics—to look at other aspects of the Austin–Reynolds study. Dr. Kupper and his associates at the University of North Carolina's Department of Biostatistics reviewed the Austin–Reynolds case–control study for accuracy of the database and statistical calculations. After validating the database and replicating the models Austin used, the North Carolina researchers carried out further extensive studies of their own by examining the suggested occupational factors. They submitted a complete report in July 1987.

The Kupper report contains many caveats and offers several possible suggestions and ideas for further investigation. This report found that three occupational factors remained robust and significant: (1) working around radioactive materials, (2) working at Site 300, and (3) working around volatile photographic chemicals.

Factors 1 and 2 were stronger in the earlier part of the study period than in the later part, with a shift possibly around 1974. The best interpretation was that the three significant occupational factors could be linked to some unknown, hypothetical factor encountered by employees. The association with the hypothetical factor might have been valid only in the early years (until 1974), or exposure to the hypothetical factor may have become less prevalent with the passage of time.

Kupper and his associates also suggested that Austin and Reynolds "overinterpreted" their study. However, they allowed that the occupational factors originally identified were the best candidates for further investigation.

Kaiser Foundation Study on Lesion Thickness

In early 1991, Dr. Robert Hiatt of the Kaiser Foundation reported on a review of slide samples given to three eminent dermatopathologists. In this blind study, the pathologists did not know where any sample came from. The study included 20 LLNL cases diagnosed between 1970 and 1984 and 36 matched control cases not from the Laboratory.

The hypothesis was that intensified surveillance by LLNL employees had resulted in an elevated incidence rate by picking up thinner, earlier lesions than were observed in non-LLNL Plan members. However, thinner lesions were only confirmed prior to about 1976, which was before all the publicity began about melanoma at the Laboratory. After 1976, the Kaiser data showed no difference in lesion thickness.

Further Studies on Lesion Thickness

Subsequently, Drs. Moore and Schneider at the Laboratory carried out an independent study of lesion thickness. Part of their motivation was that they disagreed with some of the methodological details of the Kaiser study on lesion thickness. The Moore and Schneider study supports

the possibility that surveillance bias could have contributed to the elevated rate at LLNL.

In early 1992, two coordinated studies were done at the Stanford University Medical School and at the Northern California Cancer Center. One study looked at the possibility that underreporting of community-based melanoma cases to the Tumor Registry, in contrast to aggressive case finding at the Laboratory and complete reporting to the Tumor Registry, could have contributed to the apparently elevated rate found for LLNL people. This study concluded that underreporting (an estimated 12% of community cases did not make it into the Registry) could not account for the excess at the Laboratory. The second study found that, of the individuals with melanoma reported in the Registry, those from LLNL had thinner lesions than people in the adjacent community from 1974 to 1985. Once again, this finding supports the hypothesis that increased surveillance and early detection could have contributed to the higher rate at the Laboratory.

Recent Work at LLNL

Recent statistical analyses by Dr. Moore show that the incidence of invasive melanoma at the Laboratory, the most serious form, has declined gradually and is no longer significantly elevated above the rate in the surrounding counties. The rate for noninvasive (*in situ*) cases continues to be elevated, but this finding might be expected in view of LLNL's dermatologic clinic and its policy of frequent biopsy.

Through the Laboratory's clinic, Drs. Moore and Schneider have found what appear to be significant differences in the clinical characteristics of invasive and noninvasive cases. The traditionally recognized risk factors for melanoma are:

- Hair and eye color.
- Skin type.
- Tendency to burn rather than to tan.
- Number of moles.

All these factors were elevated in the invasive melanoma cases from LLNL. However, none were elevated significantly in the noninvasive cases. This finding suggests that the population at risk for melanoma may be divided into at least two different groups in terms of risk factors. More research will be required before we can draw any conclusions about the significance of this new finding.

New Study on Melanoma in the LLNL Workforce

As our summary of previous work suggests, malignant melanoma among Laboratory employees has been rather extensively studied using a variety of methods for the past 15 years or so. Such research, plus our intensive education and screening efforts and a fairly complete database, places LLNL in a unique position to look at important aspects of this disease. Because many issues remain open to interpretation—such as the proposed links between occupational factors in the workplace and melanoma—we undertook a new investigation of the increased diagnosis of melanoma among LLNL employees.[4]

First, we wanted to match more carefully the individuals diagnosed with melanoma (referred to as cases) with controls. Thus, in picking Laboratory employees without melanoma for our study (the control individuals), we added some qualifying characteristics and matching criteria that had not been used before. Our reasoning was that previous failures to match for certain characteristics might have confounded the interpretation of the data.

On the basis of our previous work pointing to a possible split in the population that is at risk for melanoma, we also analyzed the data in several ways that had not been done before. For example, we examined the combined data for all melanoma cases (plus controls), and we also separately analyzed the data for invasive and noninvasive cases (plus their respective controls). We did this analysis to investigate the possibility that risk factors may differ among invasive and noninvasive cases. That is, by analyzing the two groups separately, we would be better able to find a risk factor that applies to invasive cases but not to noninvasive cases.

Study Design

Ours was a case–control study. In such a design, one normal individual (or control) is matched to one Laboratory individual diagnosed with melanoma (or case). All melanoma cases diagnosed among employees between January 1, 1969, and March 1, 1989 (the start of the study), were eligible. The study included 69 melanoma cases who were alive and willing to participate and 69 controls, for a total of 138 participants.

We matched the melanoma individuals for several important characteristics that were not used as criteria in previous investigations, such as the Austin–Reynolds study. We selected each "best-match"

control from LLNL employees without melanoma according to five criteria:

- Sex.
- Age.
- Years of tenure at LLNL (not used before).
- Start date at LLNL (not used before).
- Years of education (not used before).

We used three techniques to gather information about participants. The first was a questionnaire administered by a nurse. Our questionnaire assessed biological factors, including many known risk factors for melanoma such as ethnicity, hair and eye color, skin reaction to sunlight, family history, and episodes of sun burn.

Second was a thorough examination by a dermatologist. The dermatologist counted all moles larger than 2 mm in diameter. (Moles smaller that 2 mm are difficult to distinguish from freckles or other skin marks.) Recall that several studies have shown that malignant melanoma is generally associated with moles greater than 5 mm in diameter.

The third technique was an occupational interview focusing on exposures to the factors suggested by Austin and Reynolds. Each recorded interview was reviewed by a panel of three experts in occupational exposure (one expert in radiation exposure and two in chemical and other nonradiation exposures). Their task was to assess exposures to suspected occupational agents.

Results of the New Study

We found the usual associations between nonoccupational factors and risk of melanoma. Individuals with melanoma were more likely to burn than tan, tended to have more moles than the controls, and had greater sun exposure in youth than controls. We applied various tests to determine which member of a pair was the melanoma case and which was the control, based on specific risk factors. We found that two factors alone would correctly identify 71% of all melanoma cases. These factors were tanning ability and the total number of moles larger than 2 mm in diameter as assessed by a dermatologist. If we restricted this classification to only the individuals with invasive melanoma, then 85% were correctly identified by these two factors alone. Only one invasive case was incorrectly identified by these two factors. This individual had good tanning ability and relatively few moles compared to his matched control, who had more moles.

The questionnaire was also useful for classifying all case–control pairs based on the following four factors: tanning ability, amount of sunbathing between ages 15 and 25, sun avoidance during the 10 years preceding diagnosis, and hiking as a pastime. These responses correctly identified melanoma cases in 56 out of 69 pairs (81% of all types of melanoma). When amount of sun exposure based on where an individual lived was used instead of sunbathing during ages 15 to 25, these four factors correctly identified cases in 35 out of 39 pairs in which the case had invasive melanoma. Four invasive cases were incorrectly identified by applying these four factors.

Our most important result was that we found no occupational factors that were significant for melanoma risk. (The box on p. 18 describes what we mean by “significant” in the context of our study.) Table 2 shows the results of our study for the five occupational factors called “causal” by Austin and Reynolds. For comparison, this table also shows the Austin and Reynolds findings. In comparing the two sets of results, note that some of the methodological details in the two studies differed. For example, Austin and Reynolds asked, “Have you ever worked around radioactive materials?” Our panel of experts reviewed the transcript of each interview as well as detailed dosimetry records and rated exposure to radioactive materials mentioned in the interview. Any material mentioned by a subject as an exposure possibility was added to a list that eventually totaled 459 substances further classified as radioactive or not. After information was pooled and a consensus score assigned, each interviewee in our study could present additional information to be used in changing one or more scores. We also assigned separate scores for different exposure periods; for example, more than 10 years before diagnosis versus less than 10 years preceding diagnosis.

In contrast to what might be expected from the Austin–Reynolds study, individuals with melanoma in our study had slightly less exposure than controls to four of the Austin and Reynolds factors: radioactive materials, presence at the Pacific Test Site, exposure to volatile photographic materials, and chemist duties. Our melanoma cases did have slightly greater exposure than controls to one factor, presence at Site 300. However, none of these differences was statistically significant. Furthermore, a computerized review of the actual words used by melanoma

cases and controls during the occupational interview failed to show significant differences in the frequencies of words associated with any of the Austin and Reynolds factors.

Discussion of the New Findings

Our findings do not support any link between those occupational factors reported by Austin and Reynolds and the incidence of melanoma in the Laboratory workforce. How can we explain these different results? One possibility is that characteristics other than the ones investigated by Austin and Reynolds may have played an important role in producing the results that were reported. In our study, controls were matched to individuals with melanoma for two important characteristics that were not used as matching criteria in the Austin–Reynolds study. These characteristics were years of education and start date of employment at LLNL.

Several other studies of melanoma, including those of Austin and Reynolds, have reported years of education as a significant risk factor for melanoma. The hypothesis is that income increases with years of education, and increased income leads to increased leisure activities in sunny areas. People with more years of education are also likely to come from families of higher socio-economic status who can afford sunny vacations with their children and college educations for those offspring. This may be relevant because data from Australia show that exposure to intense ultraviolet rays during early teenage years is the most significant solar risk factor.[5]

By failing to match for years of education, the Austin–Reynolds study confounded this nonworkplace risk factor with the occupational factors they suggested. For example, a chemist's duties require specialized education. Thus, a risk factor associated with being a chemist may be explained, at least in part, by educational background before even taking a job.

A similar line of reasoning shows how tenure at the Laboratory is another way to explain some of the differences between our findings and earlier ones. Over the years, LLNL's

A Note About Statistical Significance and Sample Size

In fields such as epidemiology and the behavioral sciences, scientists are usually limited to studying relations that are governed by the laws of chance rather than the laws of certainty. For example, we are interested in determining whether occupational factors, like working at Site 300, are related to melanoma. The relation is not hypothesized to be a simple cause-and-effect one, for example, "all who work at Site 300 get melanoma." Rather, we want to determine whether those who work at Site 300 have a greater *chance* of developing melanoma. Thus, in our case–control study, we want to know whether *significantly* more cases than controls worked at Site 300. Statistical significance is assessed by comparing outcomes with those that could occur by chance.

In our study, we found that 27 melanoma cases, compared to 25 controls (39% versus 36% in Table 2) had work activities at Site 300. The statistician's job is to determine whether this observed difference could have occurred by chance.

To answer the question, a statistician imagines two jars filled with black and red balls. In this particular case, 37.5% of the balls in each jar are black (the average percent for cases and controls). The statistician imagines drawing a sample of 69 balls from each jar, where one sample represents melanoma cases, and the other represents controls. Now he asks the question: "How likely is it that in one sample 39% of the balls are black, while in the other 36% are black?" The statistician refers to a published chart, called a binomial distribution, to determine exactly how likely such an event really is.

According to statistical convention, an event is called "significant" (that is, unlikely to be due to chance) if it occurs less frequently than 1 in 20 times. The binomial distribution requires two input values: the number of samples drawn, n, and the probability of success, p. Statistical significance depends on the values of both n and p.

In general, the larger the sample size, n, the greater the probability that an observed difference will turn out to be significant. In our case, which is based on a sample size of 69, the observed difference of 3% (39% versus 36% or less) is very common and occurs in over 92% of the samples. Thus, the statistician concludes that the two values are not significantly different ($p = 0.92$). In other words, the observed difference is most likely due to chance rather than a difference between melanoma cases and controls.

administration and workforce have been increasingly concerned with exposure to both chemicals and ionizing radiation. This concern has resulted in more emphasis on safety and a decrease in exposure over time, so that employees with earlier start dates are likely to have had higher exposures than those with later start dates. We can demonstrate that this is true in the 138 members of our case–control study. (Although ionizing radiation and radioactive materials are perceived by the outside world as major potential hazards for employees, in fact, actual radiation exposures are generally low, with only a few exceptions, which are unrelated to status as melanoma case or control.)

By failing to match for start date, Austin and Reynolds introduced another possible confounding of exposure factors. When groups are not matched for years at LLNL, it becomes possible that this variable, may have played an important role in producing the results they reported.[6]

For example, if a melanoma case who began working at the Laboratory in the 1960s was matched to a control who began working in the 1970s, the exposures to chemicals and ionizing radiation would be expected to differ. In this situation, we would not be in a position to draw conclusions about whether a specific exposure leads to increasing melanoma risk. On the other hand, when controls are matched to melanoma cases with respect to start date, we can better determine whether specific exposures increase the risk of melanoma. Our study, which matches start dates and length of employment at LLNL, did not show significantly increased exposures to any of the factors suggested by Austin and Reynolds when we compared our melanoma cases with controls.

Conclusions

From the late 1970s to the present, almost a dozen studies have been done to understand the nature and possible causes of the increased diagnosis of malignant melanoma in the Laboratory's workforce. One of these studies suggested possible occupational factors at LLNL that might be associated with elevated rates of melanoma. We recently performed a new study using better controls to reduce sources of bias and the possible confounding of important variables. From the previous literature and our new investigation, here is a

Table 2. **Comparison of LLNL melanoma cases and controls (employees without melanoma) for exposure to five occupational factors. Whereas Austin and Reynolds found significantly greater exposure to all five occupational factors in melanoma cases compared with their controls, our current study finds no significant differences between groups. We conclude that none of these occupational factors is significant for melanoma risk. Each score is expressed as the percent of individuals within a group that was exposed to a given factor. (See the text for ways in which questions, scoring, and controls in the two studies differ.)**

	Current study		Austin and Reynolds	
Occupational factor	**Melanoma cases, % exposed**	**Controls, % exposed**	**Melanoma cases, % exposed**	**Controls, % exposed**
Radioactive materials	54	57	65	33
Site 300	39	36	58	38
Photographic chemicals	45	51	35	15
Pacific Test Site	12	16	13	7
Chemist duties	22	26	13	2
	No significant differences between cases and controls		***All differences*** between cases and controls are ***statistically significant***	

summary of what we know today:
1. No clear explanation for the increased incidence of cutaneous melanoma among LLNL workers has been discovered.
2. The high level of education in the Laboratory's workforce, which is an established risk factor for melanoma, may be an important factor that at least partly contributes to the rate elevation at the Laboratory compared to the community rate.
3. Increased awareness and understanding of melanoma by Laboratory employees and their physicians has resulted in increased diagnosis of thin lesions.
4. Enhanced surveillance probably leads to prevention of life-threatening forms of melanoma. Continued monitoring of mortality from melanoma is being done to verify this belief.
5. After reaching a peak in the 1980s, the rate for invasive melanoma at the Laboratory has gradually returned to that of the community. Noninvasive melanoma, however, continues to be increased at LLNL.
6. Despite many investigations over the years, no occupational factor in the LLNL workplace has been clearly implicated or even established as biologically plausible.
7. Cancer in general (all types except melanoma) is not elevated in LLNL employees above rates in the Bay Area population.

Key Words: melanoma—incidence of, *in situ,* invasive, malignant; moles; skin cancer.

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6. Austin and Reynolds did consider length of employment as a possible risk factor and did not find it "significant" based on comparing all controls with all cases. This approach is considered to be a weaker method of controlling for confounding factors than case–control matching used in the current study.

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Center for Healthcare Technologies

We are creating a center that will coordinate ongoing Laboratory research aimed at developing more cost-effective tools for use by the healthcare community. The new Center for Healthcare Technologies will have many long-term benefits for the region and the nation.

In the U.S., we now spend about 13% of the gross domestic product (GDP) on healthcare. This figure represents nearly $3000 per year per man, woman, and child. Moreover, this expenditure is projected to grow to about 20% of the GDP by the year 2000.[1] Medical research and development accounts for only about 3% of national healthcare spending, and technology development represents only a small fraction of that 3%.

New technologies that are far more cost-effective than previous ones—such as minimally invasive surgical procedures, advanced automated diagnostics, and better information systems—could save the nation billions of dollars per year to say nothing of the potential reductions in pain and suffering. A good example of how improved technology can benefit the individual is the portable blood-glucose testing meter now available to diabetics. This quick and convenient self test costs only a few dollars and can be used daily at home, whereas each standard laboratory test costs $25 to $40 and requires a special trip to a medical facility.

Over the last decade, many projects exploring improved or new healthcare technologies have evolved from diverse and often independent research efforts at LLNL. *Energy and Technology Review* has described some of these remarkable advances.[2] We have shown how Laboratory researchers are developing better imaging systems, such as pulsed x-ray lasers and prototype components required for fully digital screening mammography. We are constantly improving the instrumentation and information systems required for genetics research, and, in the process, we discovered the gene associated with myotonic dystrophy. Using improved sensor and detection systems—accelerator mass spectrometry (AMS) in particular—we can now reliably detect trace chemicals in biological samples at levels that previously could not be measured.

Table 1. **This table shows the broad spectrum of LLNL healthcare projects outside the Biology and Biotechnology Research Program, where studies on genetics and cancer risk and prevention are ongoing. Many of the following projects are interdisciplinary in nature and most involve external collaborators.**

LLNL discipline	Project description
Chemistry and materials science	Osteoporosis research X-ray computed tomography to characterize tooth decay Clinical application of lasers to tooth root dentin
Computations	Models for neuromuscular function of the human hand
Defense-related research	New ways to measure oxygen in blood Image enhancement of chest x rays Optical laser imaging of teeth Short-pulse tissue removal Short-pulse, broadband imaging of soft tissue Noninvasive blood monitoring
Energy	Magnetic resonance imaging devices Radioactive medicinal drugs as tracers
Engineering	Studies on incipient failure in a new heart valve X-ray spectra for dose-efficient imaging Antiscatter grid for improved mammographic imaging Microtechnology for clinical instrumentation Crash and impact injury effects
Engineering, biology and biotechnology	Advanced microinstrumentation Microfabricated instruments for polymerase chain reaction Digital mammography for early cancer detection Biological sample analysis using diode lasers Computer-aided diagnostics in mammography
Engineering, biology and biotechnology, chemistry and materials science	New biocompatible materials for use in prosthetic devices (e.g., artificial joints and bone)
Lasers	Microthin lens for opthamology Lasers for surgery and photodynamic therapy Lasers for medicine X-ray lasers for biomedical applications
Physical sciences	Tritium sample chemistry for biomedical AMS ^{3}H and ^{41}Ca as tracers for biomedical applications of AMS Medical applications of computational physics Biomedical and environmental isotope tracer research Modeling studies for radiation therapy X-ray lasers for biological microimaging
Health services	Digital vibrogram to test for carpal tunnel syndrome

These and scores of other approaches can potentially improve the healthcare of millions of people.

The scope of LLNL's work in the area of healthcare technology has increased in recent years. Our Biology and Biotechnology Research Program has major efforts in genetics research and instrumentation and in the causes and prevention of cancer. In addition to these important efforts, Table 1 shows the large number of currently funded projects now under way in other disciplines at the Laboratory. Most of these projects involve one or more university collaborators or industrial partners.

In late 1992, LLNL Director John Nuckolls addressed the need to explore a more coordinated effort in the field of healthcare technology. In August 1993, Tony Carrano, Associate Director for the Biology and Biotechnology Research Program, formed a Healthcare Technology working group. Today, we are creating a new cross-disciplinary center at LLNL, to be named the Center for Healthcare Technologies (CHT).

The CHT will focus on cost-effective, high-technology healthcare products and systems that can be made available to all. A primary mission for the Center will be to explore the ways in which the Laboratory can become a leader and catalyst for healthcare technology development.

The benefits of the CHT will be felt at the national, regional, and local levels. At the national level, we will provide better healthcare tools at lower cost. At the state level, we want to spark healthcare technology sectors in California and further our working alliances with medical researchers at institutions such as Kaiser Permanente, Stanford University, UC Davis, UC San Francisco, and many others. For the Laboratory itself, the CHT can help create new research programs and serve as a model for coordinating projects that, by their very nature, will continue to span many different programs.

Key Words: accelerator mass spectrometry (AMS); Center for Healthcare Technologies (CHT); digital mammography; genetics research; healthcare; pulsed x-ray imaging.

Notes and References

1. Projections for healthcare expenditures in the next century are from "The National Health Care Phobia," *Newsweek*, September 6, 1993, and *Technology Review,* October 1993.
2. For a description of digital mammography, see the October–November–December 1992 issue of *Energy and Technology Review* (UCRL-52000-92-10/11/12), pp. 27–36; for a capsule summary of advances related to accelerator mass spectrometry and pulsed x-ray laser imaging, see the January–February 1994 issue of *Energy and Technology Review* (UCRL-52000-94-1/2), pp. 30–35; for improved diagnostics and instrumentation in the field of genetics, see the April–May 1992 issue of *Energy and Technology Review* (UCRL-52000-92-4/5), pp. 29–62; for improved computer detection of features in biomedical images, see the May 1993 issue of *Energy and Technology Review* (UCRL-52000-93-5), pp. 7–13.

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Abstracts

Forensic Science Center

The Laboratory's Forensic Science Center serves as a focal point for a comprehensive forensic approach to sample analyses. The Center can completely characterize almost any sample—soil, gas, liquid, or vegetation—with a suite of analytical technologies. The analyses requested by various clients to date have included high explosives, chemical-weapon-related compounds, genetic material, nuclear species, and narcotics. Detecting, analyzing, and interpreting the presence of these and related compounds, from macroscopic (grams) to ultratrace (picograms) concentration levels, are the principal strengths of the Center.

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Melanoma at LLNL: An Update

From the late 1970s to the present, almost a dozen studies have been done to understand the nature and possible causes of the increased diagnosis of malignant melanoma in the LLNL workforce. Some of these studies have suggested possible occupational factors at the Laboratory that might be associated with elevated rates of melanoma. However, a recent study initiated by LLNL, which uses better controls than before, fails to support any link between occupational factors and the incidence of melanoma in the Laboratory workforce. It is possible that the high level of education in the Laboratory's workforce—an established risk factor for melanoma—may play a role. After approaching a peak in the 1980s, the rate for invasive melanoma at LLNL has gradually returned to that of the community. Noninvasive melanoma, however, continues to be increased at the Laboratory. Enhanced surveillance probably leads to the prevention of life-threatening forms of melanoma. Continued monitoring of mortality from melanoma is being carried out to verify this finding.

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Center for Healthcare Technologies

The Laboratory has created a new cross-disciplinary center, the Center for Healthcare Technologies, to focus on developing cost-effective, high-technology healthcare products and systems. The benefits of this Center will be felt nationally, regionally, and locally. At the national level, we will provide better healthcare tools at lower cost; at the state level, we hope to spark healthcare technology sectors in California and further our working alliances with nearby medical research institutions; and at the Laboratory, we will create new multidisciplinary research programs.

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