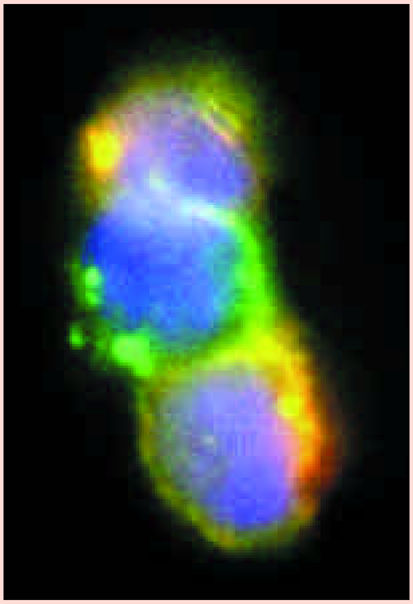
DATELINE LOS ALAMOS

U.S. DEPARTMENT OF ENERGY
UNIVERSITY OF CALIFORNIA

NEW TESTS WILL HELP PREDICT, DIAGNOSE CHRONIC BERYLLIUM DISEASE

BLOOD TEST IDENTIFIES SENSITIVITY; GENETIC MARKERS INDICATE INCREASED RISK



Three lymphocytes isolated from blood and stained with fluorescent tags for analysis in the Immuno-LPT.

A two-pronged research effort will make it easier to identify people sensitive to beryllium metal and help prevent workers from developing Chronic Beryllium Disease, a disabling and sometimes fatal lung condition. It is estimated that several thousand people in the United States work with beryllium, a unique metal used in nuclear weapons and, in the commercial sector, for telescope mirrors, golf clubs and a host of other applications.

A team led by Babs Marrone of Los Alamos' Bioscience Division has devised a new, more accurate blood test to identify workers who are sensitized to beryllium. The researchers also have pinpointed genetic markers that indicate increased risk for a small number of workers who are more likely to develop CBD. The new blood test and the separate test for genetic markers, when used together, will help predict and diagnose CBD and help prevent the disease.

Roughly 3 to 4 percent of all people are at risk for serious illness from working with beryllium, although the risk is higher for some workers such as machinists. If they inhale beryllium metal in powder form, they can become sensitized to beryllium; that is, their immune systems become allergic when beryllium enters their bodies. Beryllium sensitization can be an early sign of CBD and symptoms may not appear for more than 10 years after exposure to the metal. There is no known cure for the disease.

"Sometimes people call beryllium sensitization an allergy, but it's not like ragweed," Marrone said. "The so-called allergic mechanism found in CBD is a cell-mediated immune response, with a delayed reaction to the allergen. A variety of biochemical events at the molecular level contribute to this immune response. Our blood test identifies these molecular events."

CBD is accompanied by increased beryllium sensitization, which currently can be detected with a blood test called the Lymphocyte Proliferation Test, or LPT. However, not everyone who tests positive for beryllium sensitization on the blood test will develop CBD. The psychological impact of testing positive is high, especially because it can take many years to develop CBD after first exposure to beryllium. What is needed is a blood test that better predicts CBD.

Los Alamos' new test, called the Immuno-LPT, takes advantage of the fact that both sensitization and CBD are responses to beryllium by the immune system.

A specific lymphocyte, the T helper, or CD4+ cell, is implicated in CBD. Using flow cytometry, a laser-based cell analysis technique developed

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DATELINE: LOS ALAMOS

and refined over many years by Los Alamos, the Immuno-LPT detects proliferation of the CD4+ cells in response to beryllium. The Immuno-LPT shows that people who have CBD typically show a CD4+ cell response to beryllium. However, some people who are sensitized but don't have CBD may have another type of response involving proliferation of T-suppressor or CD8+ cells.

A team led by researcher Babs Marrone has devised new blood and genetic tests that predict Chronic Beryllium Disease, a sometimes fatal lung condition.

The results suggest that individuals who have CD4+ cell proliferation in response to beryllium have the greatest likelihood of developing Chronic Beryllium Disease, because their responses match those seen in CBD. So the Immuno-LPT may be more accurate than the current test in predicting whether someone will develop CBD.

Scientists have long suspected that a genetic risk factor for CBD makes certain individuals more likely to develop sensitivity and disease when they become exposed to even small amounts of beryllium. Such an effect may explain why CBD is seen in some people with minimal exposure to beryllium, and also why many with high exposure don't develop CBD.

Los Alamos researchers now can locate genetic markers that are present in individuals with CBD but absent in others who don't have the disease. The researchers' goal is to identify a panel of markers and the degree of risk associated with each.

Several years ago, researchers discovered tantalizing evidence of a possible genetic marker, called Glu69, for susceptibility to Chronic Beryllium Disease. Their discovery couldn't be used to help workers because the marker they identified also occurred frequently in a control population. When projected to the general population, the marker might be present in one in three people who are not susceptible to the disease.

"We've been able to pull apart these two populations a lot better," Marrone said. "We looked more closely at the alleles, the region of the genome around the marker, and we found other contributing genetic factors that help us pinpoint those who are at risk."

For CD4+ cells to proliferate in response to beryllium, the beryllium must be "presented" to them by protein molecules called Human Leukocyte Antigens factors. Slight differences in the DNA sequence of the gene responsible for making the HLA protein often are found in individuals with CBD. The responsible gene is located on chromosome 6.

Because these differences are inherited and not caused by beryllium exposure, researchers could use the genetic markers to identify individuals with greater susceptibility to develop beryllium disease. Beryllium workers with greater genetic risk could make more informed decisions about whether they should work with beryllium. They also could be placed on more intensive medical surveillance.

Marrone and her colleagues are working with industrial hygienists, physicians, environmental scientists, chemists and health physicists to better understand how beryllium damages the immune system, with the ultimate goal of a cure for beryllium disease. Experts in legal and ethical issues also seek to integrate new information about genetic markers into beryllium medical surveillance practices.

Los Alamos, Lawrence Livermore and E.O. Lawrence Berkeley national laboratories are working with the University of California Operations Office and the Department of Energy on a plan to implement a Chronic Beryllium Disease Prevention Program.

“We hope to integrate the new tests into this implementation plan, which will provide Los Alamos workers with the most advanced technology available for beryllium health surveillance,” Marrone said.

Los Alamos has been conducting tests across the DOE complex for four years. Marrone predicts that the testing technology will be ready to transfer to industry in about a year and that the tests will be simple enough to be run by any diagnostic lab.

Results of initial Immuno-LPT studies were published in February in the journal *Toxicology*. An initial research paper on the genetic markers was published last August in an issue of *The Journal of Immunology*. Researchers from Oak Ridge National Laboratory and the National Jewish Medical and Research Center in Denver collaborated with Los Alamos on the studies.

Funding has been provided by the DOE’s offices of Biological and Environmental Research and Occupational Medicine and Medical Surveillance.

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DATELINE: LOS ALAMOS

DEVICE $AVES MILLIONS

MONITOR CAN DETECT TINY AMOUNTS OF RADIATION IN LARGE CRATES OF WASTE

A device that measures radioactive waste is so sensitive it will be able to find the radioactive equivalent of half a packet of sugar sprinkled into a waste crate. The garage-sized Crated Waste Assay Monitor, or CWAM, will save the Department of Energy and its subcontractors almost $4 million a year.

The CWAM uses a neutron-activation system to “look” into 4-by-4-by-6-foot steel boxes that contain a variety of nuclear-weapons factory wastes. Once its 5-ton door closes over the box-analysis area, CWAM fires neutrons into the waste and reflects the resulting signal from arrays on all six sides of the waste crate, a technique known as active interrogation.

The radioactive contents of an entire box can be analyzed in 30 minutes with the technique. Sensitive detector arrays, combined with specialized software packages, determine the source, matrix type and source location in the crate from the returned neutron signal.

The process, called the Differential Die-away Technique, allows operators to determine the amount of uranium or plutonium inside each

A sample waste crate is loaded into the Crated Waste Assay Monitor at Los Alamos. CWAM has since been disassembled and shipped to its new home at the Y-12 plant in Oak Ridge, Tenn. With estimated savings of nearly $4 million a year and based on a development cost of $2.8 million, CWAM will have paid for itself by December.

box, despite a potentially dense matrix of scrap metal, baled debris and other waste materials.

In its new home at the DOE's Y-12 plant at Oak Ridge, Tenn., it will be used primarily for uranium detection.

"Correcting for the dense matrix of other materials is one of the key advances in this technology," said Los Alamos developer Sheila Melton. "The operator can confidently determine from the readings an amazing amount of detail. For example, CWAM can distinguish a large, shielded piece of uranium in the center of the box from several smaller pieces of the metal near the edges, information needed to correctly categorize the waste for efficient, legal disposal."

With that level of detail, Y-12 technicians can safely analyze approximately 1,000 crates per year that await disposal at the facility, and they can determine which are below the regulatory limit. Boxes containing less than one ten-billionth of a Curie of uranium per gram of waste can be disposed of at the Y-12 site landfill. Without the CWAM measurement, the waste would have to travel to an offsite radioactive waste facility at considerably greater cost.

CWAM's effective differentiation of waste bound for onsite vs. offsite disposal has a significant financial impact. Including transportation, disposal, container and characterization costs, the annual savings to the public is $3.7 million, assuming a throughput of 1,000 boxes per year.

The system was developed with the support of the DOE's Office of Nonproliferation and National Security, the Office of Security and Emergency Operations and the Technology Development Program, and Canberra Industries, a nuclear systems and instrument company based in Meriden, Conn. Canberra Industries will be in charge of operating the device at Y-12.

The CWAM system will serve as the prototype for another combined neutron and gamma ray measurement system designed to assay low-level and transuranic nuclear waste. The next-generation instrument, called the Integrated Box Interrogation System, can be used at nuclear facilities nationwide that require accurate analyses of radioactive waste.

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DATELINE: LOS ALAMOS

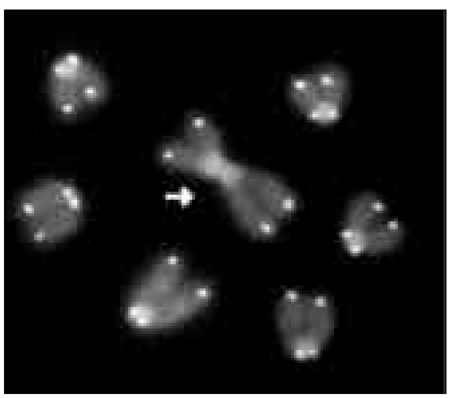
AN 'INTRIGUING PARADOX'

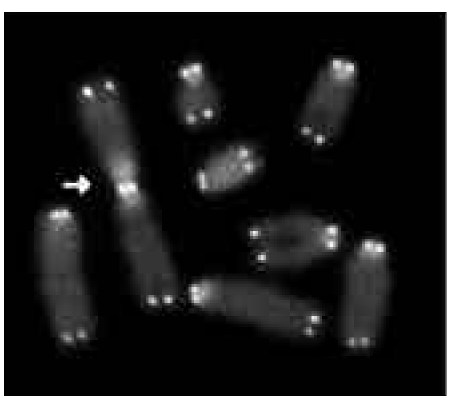
DNA REPAIR PROTEINS FOUND AROUND UNBROKEN ENDS OF TELOMERES

Surprising new discoveries about telomeres — the ends of chromosomes — one day may lead researchers toward new paths in cancer research and a better understanding of the biology of human cells.

Telomeres are known to have important roles in the development of cancers and in the aging process. They are nucleic acid/protein structures that act as "caps" to prevent the DNA in these chromosomal regions from degrading.

A team of researchers from Los Alamos and E.O. Lawrence Berkeley national laboratories and the Memorial Sloan-Kettering Cancer Center in New York has found that, for reasons still unknown, specific DNA repair proteins typically found around broken DNA ends also surround mammalian telomeres, which are natural ends. Moreover, these repair proteins are required to maintain normal mammalian telomere functions.





The mouse chromosomes in the top image contain the repair protein. No telomeres are present at the point of fusion (shown to the right of the arrow). The mouse chromosomes in the lower image are deficient in the repair protein and telomeres are obvious at the point of fusion (to the right of the arrow).

The presence of the repair protein called DNA-dependent protein kinase, or DNA-PK, somehow plays a key role in preventing chromosomes from "fusing" together end-to-end. Chromosomal fusions cause cellular instability (problems when the cell tries to divide) and can lead to cancer.

When two chromosomes join at the ends, they fuse together and essentially create one long chromosome with two centromeres, regions of chromosomes that play important roles in cell division. When cell division occurs shortly afterward, the new cell typically is unstable, either because it has too much genetic material (too many centromeres) or not enough.

If the unstable cell dies, then nothing else happens. If it remains alive, however, the potential for the development of tumors or various cancers increases significantly.

In research published in the December issue of *The Proceedings of the National Academy of Sciences*, the team reported that in controlled laboratory tests using a telomeric detection technique called fluorescence *in situ* hybridization, the telomeres still were present after fusion occurred in mouse chromosomes lacking DNA-PK. This finding refuted previous reports that fusion occurred only in the absence of telomeres, which can break off from chromosomes as a result of radiation exposure, oxidative damage or other ways.

The researchers also discovered that compared with mouse chromosome samples containing normal levels of DNA-PK, telomeric fusion occurred only in the protein-deficient samples, demonstrating that these proteins are necessary to prevent telomeric fusion in mammalian cells.

The researchers' findings, however, present them with what they call an "intriguing paradox." Logically, there is no reason for DNA proteins to be present around telomeres, because they are not broken ends. Further, there is no reason to suspect that DNA repair proteins would be required to maintain normal telomeric functions.

Through some unknown mechanism, the repair proteins allow a cell to recognize telomeres as natural ends and not broken DNA strands in need of repair. Additional studies are under way to try to solve these mysteries.

Funding for the research was provided by grants from the Department of Energy, U.S. Army and National Institutes of Health.

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DATELINE: LOS ALAMOS

MAKING IT SAFER FOR EMERGENCY CREWS

MODELING TOXIC RELEASES IN URBAN SETTINGS LEADS TO 'RULES-OF-THUMB' DOCUMENT ON WEB

High-tech mapping of the winds in "urban canyons" is bringing a new level of safety to firefighters, police, medical teams and others who respond rapidly to emergencies where hazardous materials may be present.

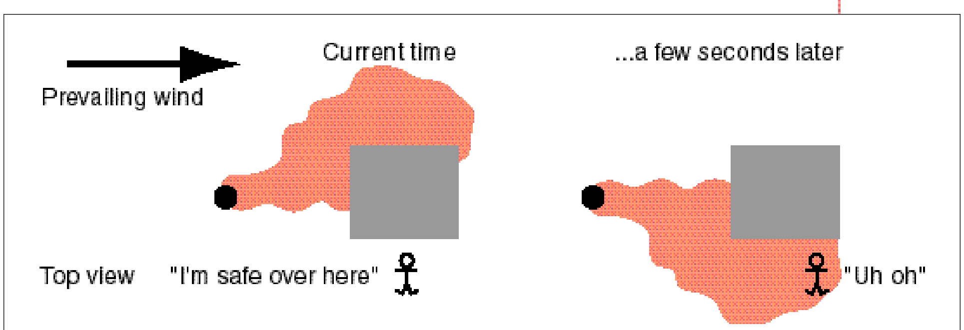
Scientists are using Los Alamos supercomputers and wind tunnels to perfect their understanding of the eddies and transport of airborne particles of chemical or biological hazards in cities, parks and even inside buildings. The information is proving vital to emergency crews as they plan routes for civilian escape and their own responses.

A team from Los Alamos, the National Oceanic and Atmospheric Administration and Lawrence Livermore National Laboratory has been confirming the accuracy of computer-simulated wind flow and particle dispersion by comparing its computer models to actual wind-tunnel experiments, and already a "rules-of-thumb" document for emergency responders is available on the World Wide Web.

In the short time that the rules-of-thumb document has been online, officials from several agencies have applauded it, including the Los Angeles County Fire Department, the U.S. State Department, the International Association of Fire Chiefs and a consultant for the Federal Emergency Management Agency.

The effort, part of the Department of Energy's Chem-Bio Non-Proliferation Program, is aimed at mapping how air flows in the complex shapes

Small-scale wind variability: The local wind can switch direction very rapidly, so that the plume may switch from one side of the building to the other in a matter of seconds. Lesson: Because of the turbulent nature of the wind, it is very common for a plume to bounce from one side of the building to the other; hence, don't assume that you are safe on one side of the building just because the plume is currently on the other side.



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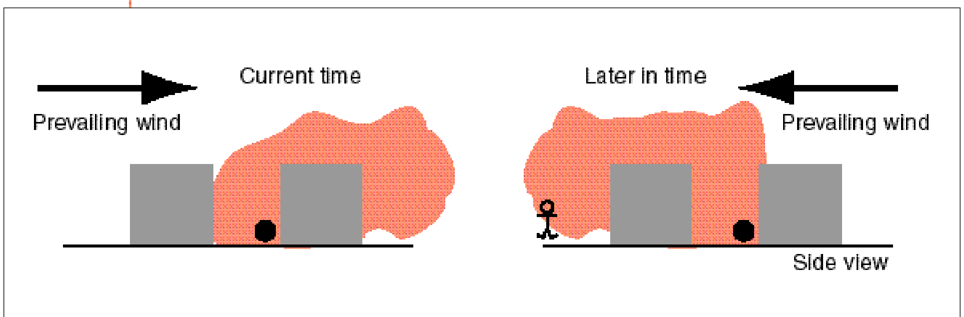

Large-scale wind variability: The prevailing wind switches direction occasionally, so that the upwind safe zone may now be downwind. Lesson: The prevailing wind is not fixed and under some circumstances can change direction quickly; thus, monitor the prevailing wind direction so that safe zones can be maintained.

of manmade environments. By comparing the virtual air flows on the computer to those actually visible in a wind tunnel at the Environmental Protection Agency's Fluid Modeling Facility at Research Triangle Park, N.C., researchers can see how close to the mark their computer results might be.

Pinning down these flow patterns has a direct application in the real world, where police, fire and other emergency crews may need to respond to a chemical or biological agent release. Knowing something as essential as whether to stay indoors or out, on the east or west side of a building, or at floor or roof level can be lifesaving information. Development of a publicly available document and the continuous improvement of the computer models take on more than theoretical importance.

The document, 'Emergency Responders' "Rules-of-Thumb" for Air Toxics Releases in Urban Environments,' is on the web at the following address: http://www.lanl.gov/orgs/tsa/tsa4/aquality/chbio.html.

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DATELINE: LOS ALAMOS

NEW EYE IN THE SKY

MULTISPECTRAL THERMAL IMAGER CALIBRATED AT LOS ALAMOS IN UNIQUE CRYOGENIC VACUUM CHAMBER

When the Los Alamos-designed Multispectral Thermal Imager satellite took its place in low-Earth, polar orbit last month, researchers and analysts from a wide range of scientific disciplines began an eager watch for the first image data. Not that the Earth hasn't been imaged, mapped and examined before, but the unique MTI telescope will provide day and night scenery shown across 15 spectral bands, or colors, ranging from the visible to the long-wave infrared.

The carefully selected visible and infrared spectral bands will allow researchers to measure the atmosphere between the ground scene and the satellite and to look for subtle attributes of the scene. Specific science tasks will include analyzing surface temperatures, water quality and even vegetation health.

MTI is a research and development project sponsored by the Department of Energy in support of the nonproliferation and national security mission. It is a joint project of Los Alamos and Sandia national

Bill Atkins rolls the satellite out of the thermal chamber during calibration last year at Los Alamos.

laboratories and the Savannah River Technology Center. Its design is based on detailed physics-based modeling and analysis performed at Los Alamos and engineering by Sandia. Major industrial partners include Ball Aerospace, TRW, Santa Barbara Research Corp. and Hughes Danbury Optical Systems.

The satellite system was integrated at Sandia and was launched March 12 from Vandenberg Air Force Base in California aboard an Orbital Sciences Corp. Taurus rocket, funded by the U.S. Air Force.

Calibration of the highly precise imaging equipment for MTI presented a unique opportunity for scientists and technicians at Los Alamos, who worked with the National Institute of Standards and Technology to develop a technical resource that has reached new levels of calibration accuracy. The calibration laboratory is part of Los Alamos' Space and Remote Sensing Sciences Group.

Using a specially developed thermal vacuum tank and liquid-nitrogen cooling at minus 320 degrees Fahrenheit, researchers simulated the frozen, airless conditions of space, perfecting the satellite's ability to take accurate measurements. NIST has since adopted the design of the infrared source and will use it in its new Advanced National Calibration facility in Gaithersburg, Md.

To gather its image data, MTI looks through a 36-centimeter aperture and uses a bank of three sensor chip assemblies, each carrying 15 arrays of detectors. Each array contains either 208 or 832 pixels, providing MTI with nearly 17,000 tiny detectors, each no larger than the period at the end of this sentence.

The 510-pound instrument is designed to be self-correcting in its data gathering, adjusting for the effects of clouds, water vapor and airborne particles present in each image of the ground to ensure that data analysts have full information about the factors affecting images, exactly as they are captured.

The satellite also carries a High-energy X-ray Spectrometer sponsored by the National Oceanic and Atmospheric Administration and the Czech Republic's Astronomical Institute of the Academy of Sciences. This instrument will collect data needed to better understand a rare species of solar flare associated with high-energy particle storms that can endanger astronauts and damage space equipment.

The project's three-year mission objectives are to advance basic knowledge and applications of multispectral and thermal imaging, image processing and associated technologies. Data from the satellite will be received at a ground station at Sandia, then transmitted to the Data Processing and Analysis Center at Los Alamos. The DPAC is the main data repository for MTI and also the distribution center for data and data products.

Researchers at Los Alamos, Sandia, Savannah River and other DOE facilities will compare satellite images to data simultaneously collected from volunteer U.S. sites. “We will be looking at cooperative sites that have been instrumented by Savannah River and using a combination of satellite data, ground truth data and analysis systems to validate our predictions,” said Los Alamos researcher Paul Weber. MTI will be used to study forests in Wisconsin, the Great Lakes area, Crater Lake, Lake Tahoe, oceans and even Hawaiian volcanoes, said Weber.

A MTI Users Group will allow other U.S. government-funded researchers to request specific imagery from the satellite and to use satellite data for applications such as environmental science.

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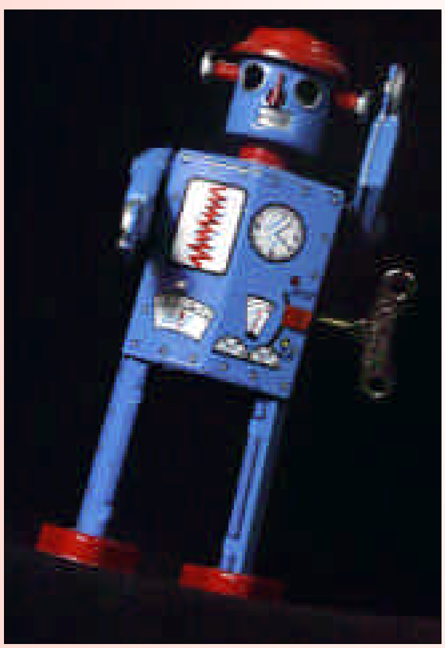
SCIENCE FOR THE 21ST CENTURY

NEW WAYS TO EXPLOIT THE CAPABILITIES OF ROBOTS

Robots have come a long way since they were introduced to the world in their modern guise as "mechanical people" in a 1920 Czech play, but if the past few years are any guide, they will go further still.

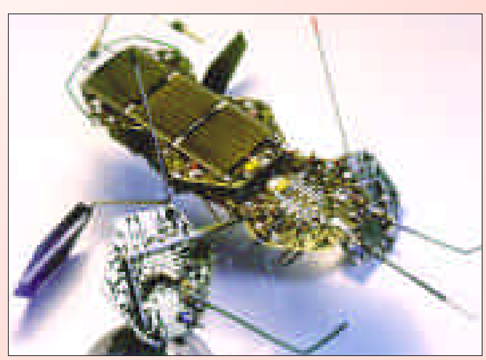
The use of industrial robots, broadly defined as devices that perform work, has grown rapidly in factories, hospitals, research laboratories and the military. In the future, they may perform surgery, continue to replace humans for hazardous tasks, become household appliances, detect and defuse land mines, help the elderly and disabled, colonize other planets and conduct large-scale biological analyses for environmental management on Earth.



Robots first found a practical use in manufacturing applications such as welding, assembly and parts inspection. Later, they "found employment" in the military and in space.

In recent years, they have been used in the medical industry, satellite systems, pharmaceutical development, entertainment and basic research.

At Los Alamos, robots and other automated devices have been used for years, primarily to transport, store and handle hazardous materials. More recently, they



You've come a long way, buggy. Robots have evolved from the "mechanical people" first introduced in the 1920s into tiny "bugs" developed at Los Alamos in the 1990s.

have helped characterize and clean contaminated equipment and soil, perform chemical analyses and laser diagnostics, and sequence basic genetic material.

Los Alamos robotics expertise is being integrated into major projects such as ARIES, a system to dismantle nuclear weapons safely; Telemed, a nationwide service providing rapid, reliable health care data to the medical community; and the National Ignition Facility, a laser fusion facility under construction at Lawrence Livermore National Laboratory.

In the future, the existing capabilities of robots at Los Alamos will be refined and expanded. Researchers also will study their potential uses in such areas as removing and cleaning contaminated filters, autonomous hazardous waste disposal, disposable sensor platforms and discovering new drugs.

Robots, most of which don't even vaguely resemble humans, generally work faster and more precisely than people, they don't get tired, and they can handle dangerous materials and work in dangerous situations. Their growing use is linked to the development of computers, sophisticated controls and other electronic equipment. Computers provide a way to control robots more precisely, allow adaptation to changing environments and, most importantly, reprogram their ability to handle more difficult, comprehensive tasks. Some researchers even define robots as the physical extensions of computers.

Other Los Alamos researchers are investigating the use of minimal autonomous robots that work without computers or human supervision, basing them on novel, fundamental principles of machine control. Such robots "learn" how to do their jobs in relatively unstructured environments, rather than being programmed for specific tasks.

Potential uses for these autonomous devices include detecting and destroying land mines, acting as tactical "scouts" in battlefield situations, cleaning areas of hazardous waste material, performing routine household tasks and investigating specific phenomena in space. In the future, autonomous robots will gain problem-solving abilities by being linked with computer-based neural networks, giving them animal-like skills to tackle real-world problems.

Robotics is taken seriously at Los Alamos, where the materials-handling requirements are among the most stringent in the world. A robot that cleans kitchen floors is nice, but a robot that handles radioactive materials safely is essential. Los Alamos will continue to take advantage of improvements in mechanized sophistication, robustness and accuracy, while pursuing research to advance the field of robotics even further.

Dateline: Los Alamos

BRIEFLY ...

LOS ALAMOS HAS AWARDED A CONTRACT TO AUSTIN, TEXAS-BASED HENSEL PHELPS CONSTRUCTION CO. TO DESIGN AND CONSTRUCT THE NONPROLIFERATION AND INTERNATIONAL SECURITY CENTER. The NISC will house most of the arms control, treaty verification, nuclear safeguards and nonproliferation functions performed by Los Alamos' Nonproliferation and International Security Division, along with about 465 of its employees. "Los Alamos is increasingly involved in the fight against international weapons proliferation and terrorism," said Don Cobb, associate Laboratory director for Threat Reduction. "The NIS Center will give us the focus and facilities needed for this important work. I am extremely pleased that both the Department of Energy and the Congress support the urgent need for NISC." Construction of the $63 million, 163,375-square-foot secure facility is slated to begin in August 2001. Completion is estimated for April 2003.

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