LOS ALAMOS NATIONAL LABORATORY
WHERE SCIENCE MAKES A DIFFERENCE

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LOS ALAMOS

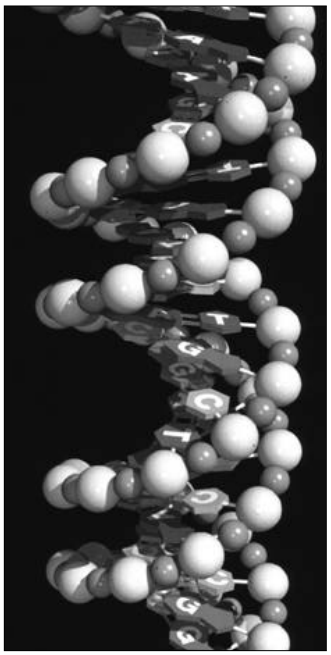
# LOS ALAMOS RESEARCHERS FINISH MAPPING HUMAN CHROMOSOME 16

## MAP WILL ACCELERATE DISCOVERY OF DISEASE GENES

Scientists at Los Alamos have completed a physical map of human chromosome 16. The map is the third to be completed as part of the Human Genome Project — an international effort begun in 1988 to map the DNA of all 22 pairs of human chromosomes plus the X and Y sex chromosomes.

DNA, or deoxyribonucleic acid, makes up the chromosomes that carry the genetic information found in all living organisms. A gene is a section of DNA that triggers cells to perform a variety of functions, or, in some cases, malfunctions.

Los Alamos' Center for Human Genome Studies (CHGS), under the direction of



A computer-generated image of DNA. The architecture of a DNA molecule resembles a spiral staircase with the stairs composed of pairings of four nitrogen-based substances.

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Robert Moyzis and Larry Deaven, began studying chromosome 16 in 1989. The chromosome contains genes involved in leukemia and other types of cancers, blood disorders, and a type of kidney disease that produces cysts on the victim's kidneys. Another gene on chromosome 16 may come into play during the later stages of breast and prostate cancer. After these types of cancers progress, a region on the long arm of chromosome 16 has been found to be deleted or lost. The researchers believe this relationship may indicate that a cancer-suppressing gene is located in this region.

The chromosome 16 map will aid scientists in their quest to locate specific genes on the chromosome and determine what genes are associated with various diseases. Identifying the genetic cause of a disease is an important step in understanding the disease and developing new ways of treating genetic disorders.

The Los Alamos team has assembled a low-resolution physical map: an array of more than 600 overlapping DNA fragments that together span chromosome 16 from one end to the other. When displayed graphically, the map covers a sheet of paper more than 18 feet long.

Each fragment, known as a YAC (yeast artificial chromosome), is a piece of human DNA hidden between two pieces of yeast DNA. The end pieces of yeast DNA fool the yeast cell into replicating the hybrid chromosome as its own. This advanced laboratory technique allows scientists to

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*EDITOR*
Diane Banegas

*MANAGING EDITOR*
Meredith Coonley
(505) 665-3982

*WRITERS*
Kathy DeLucas • James Rickman
Theresa Salazar

*PHOTOGRAPHERS*
John Flower • Fred Rick
LeRoy N. Sanchez • Mark Tilden

*ILLUSTRATORS*
Mel Prueitt • Edwin Vigil

*PRINTING COORDINATOR*
G.D. Archuleta

*COMMUNICATIONS ARCHITECT*
Jeff Wollman

LOS ALAMOS NATIONAL LABORATORY
PUBLIC AFFAIRS OFFICE, MS P355
LOS ALAMOS, NM 87545

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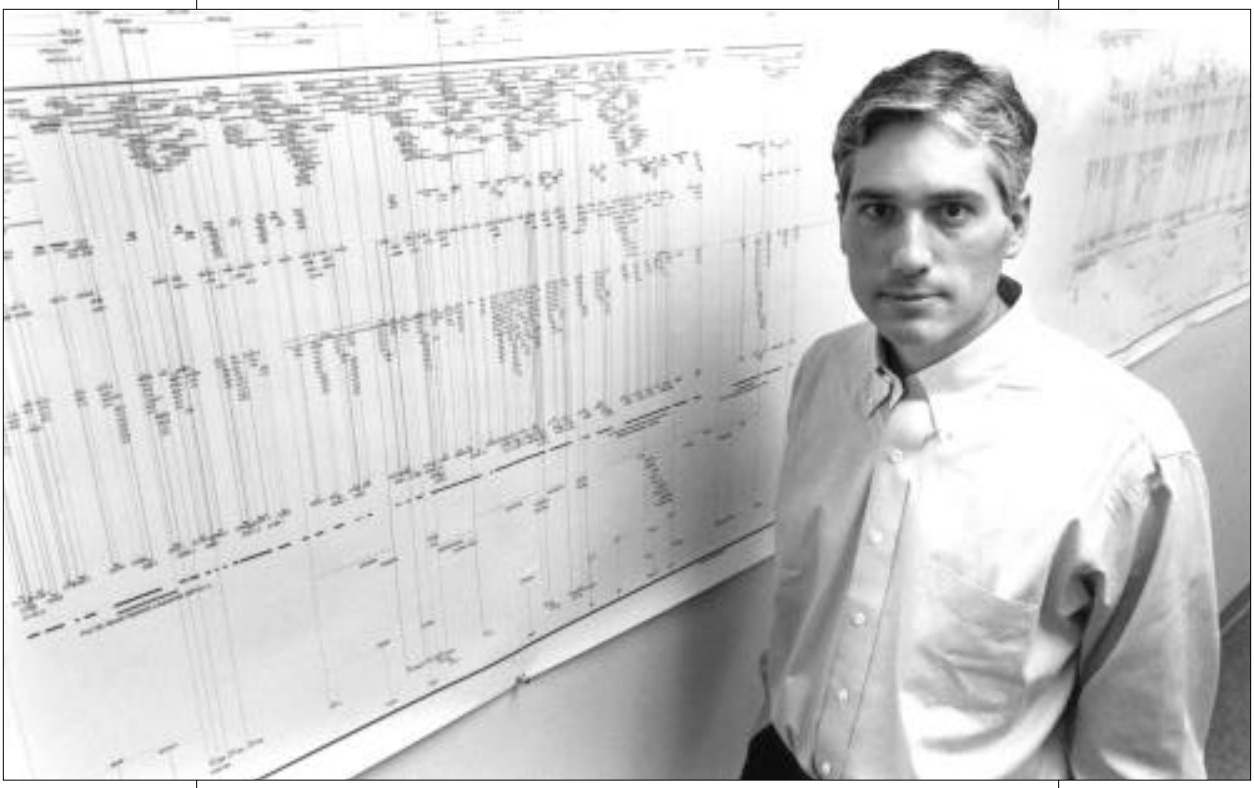

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Norman Doggett in front of the 18-foot-long physical map of human chromosome 16. Doggett led the Los Alamos team that assembled the low-resolution component of the map, which is two to three times larger than previously mapped chromosomes. The majority of the map is at a resolution more than 100 times greater than anything previously achieved.

maintain "libraries" of human chromosomes by cloning single chromosomes of human DNA as many artificial chromosomes in yeast.

Each YAC segment is marked with a tag site — a DNA sequence that appears only once on the chromosome. From these tag sites, the scientists can determine how YAC fragments overlap with one another. The result is a physical map of overlapping DNA fragments integrated with known genetic markers. The entire process is like putting together an extremely big and difficult jigsaw puzzle once you've obtained all the pieces.

A low-resolution map depicts major landmarks on the chromosome, like a road map showing major cities and highways. Another type of chromosomal map, known as a high-resolution physical map, describes the chromosome in much greater detail — like a map that shows small towns and hamlets and two-lane roads in addition to major cities and highways.

High-resolution maps are constructed from strands of human DNA that have been inserted in bacterial cells and cloned in much the same way as YACs. However, the pieces of human DNA — known as cosmid clones — are much smaller than those in YAC libraries. The two methods of cloning are complementary.

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The advantage of YAC cloning is that with larger pieces of DNA, scientists don't need as many clones and the libraries are easier to manage; however, the smaller pieces of DNA present in cosmid libraries allow scientists to construct the much more finely detailed, high-resolution maps of human chromosomes. The Los Alamos CHGS is completing a high-resolution map of chromosome 16 that shows the chromosome in hundreds of times more detail than anything previously achieved.

Los Alamos researchers Patricia Medvick and David Bruce prepare a gridding robot for its designated task of transferring bacteria cells cloned for known fragments of human DNA from their storage sites to specific locations on a grid. Gridding robots were developed at Los Alamos. A new generation of the gridding robot is now in operation at Los Alamos. It frees a laboratory technician to do other related work and is speeding completion of the Human Genome Project.

Cosmid libraries also are well-suited for determining the sequence of the base pairs in a DNA molecule. The architecture of a DNA molecule resembles a spiral staircase with the stairs composed of pairings of four nitrogen-based substances. Determining the sequence of these bases for each human chromosome is the ultimate goal of the Human Genome Project.

As part of the mapping process, researchers in the Los Alamos CHGS discovered that chromosome 16 contains a large number of base-pair sequences that are repeated over and over along the chromosome. Scientists elsewhere working on the Human Genome Project have encountered similar repeating sequences, known as low-abundance repetitive DNA, but chromosome 16 appears to have more of these repetitive sequences than other chromosomes.

The repetitive sequences have complicated the mapping process because they lead to false overlaps of DNA fragments. In spite of their troublesome nature, the repetitive sequences interest scientists because some of them are subject to rapid mutations or play a role in chromosomal rearrangements. Either scenario can lead to the onset of genetic diseases.

The Los Alamos CHGS also is mapping chromosome five. Funding for the Laboratory's work on the Human Genome Project comes from the Department of Energy.

CONTACT: NORMAN DOGGETT
CENTER FOR HUMAN GENOME STUDIES
(505) 665-4007

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# GENE LIBRARIES ARE A KEY RESOURCE FOR GENETIC MAPPING

## LIBRARIES AID SCIENTISTS IN IDENTIFYING DISEASE GENES

The recently completed National Laboratory Gene Library Project will be a boon to geneticists and other scientists in universities, hospitals, and industry who require pieces of human DNA to map chromosomes or identify disease genes.

Scientists working in the Gene Library Project at Los Alamos and Lawrence Livermore national laboratories have constructed three dozen separate libraries, each a collection of DNA fragments that span an entire chromosome. The libraries will give researchers a key resource for genetic mapping projects. These libraries also will aid scientists in their search to identify and isolate specific genes linked to inherited diseases. DNA fragments from the project are being shipped to commercial companies for duplication and distribution.

A unique aspect of the Gene Library Project was the separation of human DNA into 24 different libraries: one for each of the 22 human chromosomal pairs, plus one each for the X and Y sex chromosomes. Collectively, the fragments contain all the DNA found in humans.

Los Alamos researcher Evelyn Campbell performs a quality control step to ensure a gene library's completeness.

The gene libraries already have played principal roles for scientists constructing maps of human chromosomes 16 and 19. In addition, library fragments helped researchers isolate the genes that cause cystic fibrosis, muscular dystrophy, Huntington's disease, and breast cancer.

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Scientists working on the Human Genome Project have perfected a number of tools and techniques that have made the job of constructing gene libraries easier. Larry Deaven is the deputy director of Los Alamos' Center for Human Genome Studies.

Construction of early libraries began about 10 years ago. However, in the last 5 years, Los Alamos and Lawrence Livermore national laboratories constructed a second set of DNA libraries that were especially useful because they contained larger DNA fragments than the earlier libraries did.

These larger fragments are more helpful to scientists because they contain more base pairs — the chemical sequences that comprise DNA. The large fragments can be overlapped with other fragments and the matching base pairs lined up, allowing researchers to reconstruct regions of the DNA in a particular chromosome. The fragments also can help scientists zero in on specific genes, which are base-pair sequence subsets on DNA molecules.

Because the library fragments range from 35,000 to 45,000 base pairs long (early fragments were about 9,000 base pairs long), scientists can fit fewer pieces together to find out what the puzzle looks like. The difference is analogous to constructing a 100-piece jigsaw puzzle instead of a 500-piece puzzle. Chromosomes on the average are about 130 million base pairs long; the entire human genome contains about three billion base pairs.

Scientists working on the Human Genome Project have perfected a number of tools and techniques that have made the job of constructing libraries easier. For example, scientists can cut human DNA at specific points and then incorporate the fragments into the DNA of other organisms, such as yeast or bacterial cells.

Work on the Human Genome Project at Los Alamos and Lawrence Livermore national laboratories is funded by the Department of Energy.

CONTACT: LARRY DEAVEN
CENTER FOR HUMAN GENOME STUDIES
(505) 667-3114

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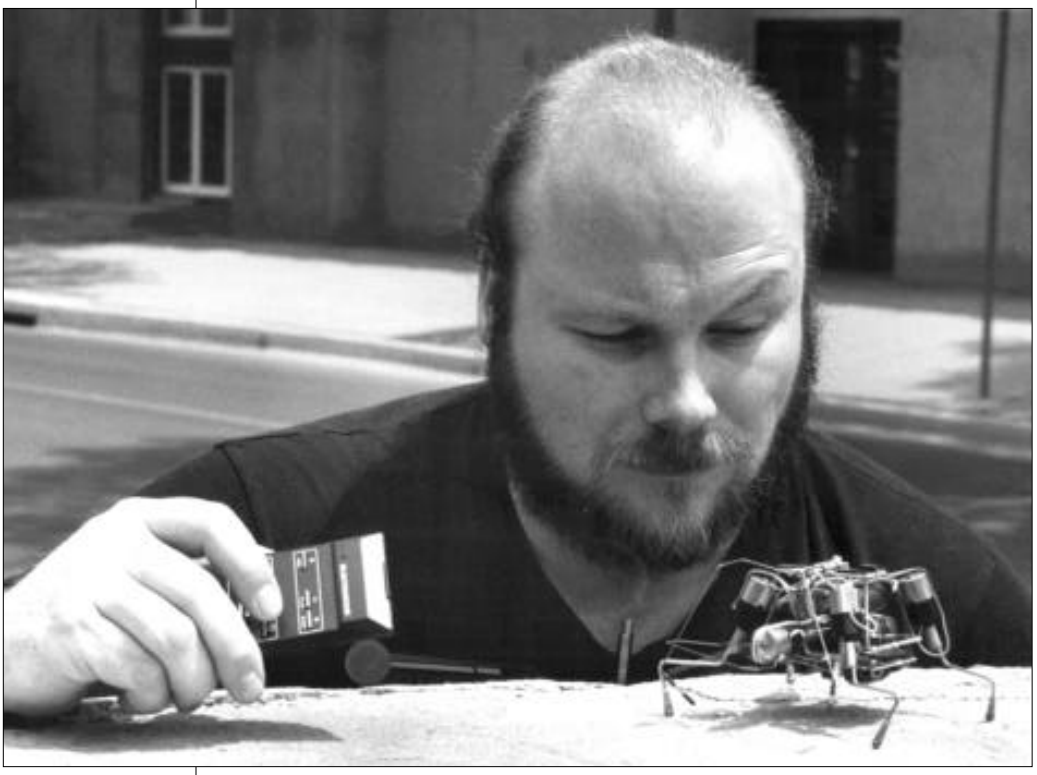
# ROBOTICS SCIENTISTS DEVELOP LIVING MACHINES

## ROBOTS SOLVE REAL-WORLD PROBLEMS AND ADAPT TO CHANGING ENVIRONMENTS

Robots of the future may come in many forms. Homeowners who hate to vacuum could own credit-card thin biodegradable robots that creep across floors eating dust. Doctors may someday prescribe pills containing tiny encapsulated robots that, once swallowed, travel to the site of a tumor and destroy it. And cars of the future may have onboard robots that steer the vehicle out of harm's way if the driver does not react quickly enough. These scenarios may sound like science fiction, but today's robotics scientists already have developed some pretty amazing forms of artificial life.



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Los Alamos researcher Mark Tilden demonstrates how the artificial central nervous system of one of his biomorphs (in this case Turtle 1.3) can adapt its gait to its immediate environment.

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Los Alamos researchers have developed "living machines," or robots, that are capable of working in unstructured, unpredictable environments. They can conduct a number of operations, including security, cleanup, and maintenance. The researchers' goal is to build robots capable of working without the need for supervision in places too dangerous or inaccessible for humans.

Tilden and various robot critters. He holds Bigfoot.

Los Alamos robotics engineer Mark Tilden and his colleagues have developed more than 80 robot prototypes and are constructing many more. Tilden's office is a "Robot Jurassic Park" filled with more than 60 solar-powered robots of 12 different species that have run continuously for more than a year. These robots have exhibited signs of fighting, sometimes in cooperative groups against their more aggressive counterparts. There even has been evidence of pecking-order dominance.

Tilden's prototypes include a battery operated "aggressive ashtray" that fires a jet of water at unsuspecting smokers, and the "solar spinner," which unobtrusively cleans windows in a stately, circular motion.

These robots, or biomorphs, are a form of parallel life. The living elements of biomorphs are not minerals, vegetables, or animals, but rather parallel aspects of all three. They have evolved from single-cell creatures to advanced insect forms like Tilden's "Walkman" robot assembled from five broken Walkman™ radios and powered by 12 transistors and one battery.

The Walkman biomorph moves on four legs and has the body structure of an ant. If the Walkman breaks a leg during its mission, it adjusts its

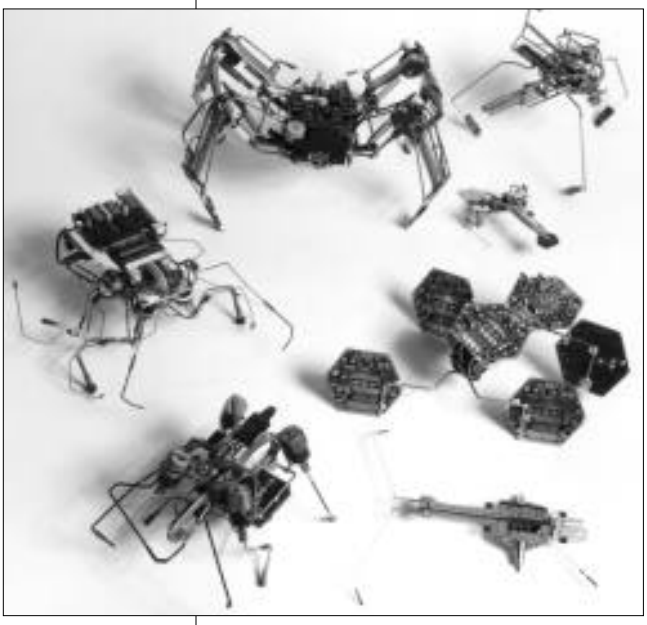
gait to walk without the damaged leg. This re-learning ability parallels the behavior of a biological bug.

The Walkman also can adjust its walking pattern to changes in terrain. The animal-like motions allow the biomorph to negotiate rather than bully its way through an environment, which will be a useful trait in future robots intended to rescue people from burning buildings or clear land mines from civilian areas.

Although still in an early stage of their development, biomorphs will in a few years be inexpensive and versatile carriers of a variety of instruments. Ultimately, these robots will do everything from seeding a wheat field to roaming terrain that is too treacherous for conventional wheeled or tracked vehicles of similar scale. Tilden and his colleagues even envision cars equipped with onboard robots that have "survival" instincts to save passengers and themselves from accidents. During a crash situation, the car would take over steering and acceleration to maximize its survival, and thus, passenger safety.

Robotics technology already has advanced to solving difficult sensory and cognitive problems. Based on principles of Artificial Life, these biomorphs exhibit characteristics that allow them to solve real-world problems in a biological manner. They do not require any form of sophisticated intelligence to function, and with no computers on board, their cost is minimal.

The model names and numbers of living machines, clockwise from top: Spyder 1.0, Thab 1.0, BEAMANT 4.0, Bigfoot 3.0, BEAMANT 3.1-12, Turtle 1.3, and Lobster 1.2, ↓



Artificial life refers to a new scientific discipline in which scientists attempt to synthesize organisms and biological systems within computers and robots for scientific study and engineering applications. One form of artificial life — known as neural networks — are computer programs that excel in solving difficult computational problems. Unfortunately, their ability to learn a simple practical skill like walking or carrying a tool is downright pathetic. Neural nets are like brains with no bodies.

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In contrast, Tilden's robots are like headless chickens with intact peripheral nervous systems. They are a form of artificial life known as Nv's, or nervous networks. Nv's can solve immediate problems of existence, although they are incapable of mimicking the brain power of a neural network. At some point in the future, Tilden predicts, neural networks will meet up with Nv's and produce the kind of thinking, ambulatory robots featured in "Star Wars."

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"Evolution of a species." The Walkman biomorph was built from five broken Walkman™ radios, 12 transistors and one battery.

Tilden's Nv research is presently concentrating on the problems of scale invariance, or the ability to make the robots function at any size. He expects the research results will prove that Nv's can work in all scales, types, and styles of robotics application. Biomorphs can then do work in the range of molecules to mountains.

Future work will concentrate on how this technology can fill the void between science fiction and reality by determining what is feasible now and then proceeding to market capable machines.

Los Alamos is seeking an industrial partner to complete the development and commercialization of this promising technology.

The Fourth Annual BEAM Robot Games held early this month at the Glorietta Conference Center in Santa Fe, N.M., featured some of Tilden's more advanced biomorphs. The games included everything from a self-starting robot dragster race to a metal micromice competition for aluminum cheese. Los Alamos sponsored this year's meeting.

CONTACT: MARK TILDEN
PHYSICS DIVISION
(505) 667-2902

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# NEW INFORMATION SYSTEM ASSISTS PHYSICIANS IN IDENTIFYING EFFECTIVE TREATMENTS FOR CHRONIC LUNG DISEASES

## TECHNOLOGY WILL IMPROVE PATIENT CARE AND LOWER TREATMENT COSTS

The prognosis is good for a new information system developed at Los Alamos and currently being tested by respiratory disease experts at the National Jewish Center in Denver. The goal of the new system, called TeleMed, is to lower treatment costs and improve patient care by dramatically improving doctors' access to patient records and past treatment histories.

TeleMed is a nationwide computer-based system that allows physicians working in hospitals and clinics to access radiographic information such as X-rays and computed tomography, or CT, scans from a national repository located at Los Alamos. The technology can give a physician a patient's complete treatment history in a few seconds, thus speeding diagnosis and treatment and reducing treatment costs by thousands of dollars.

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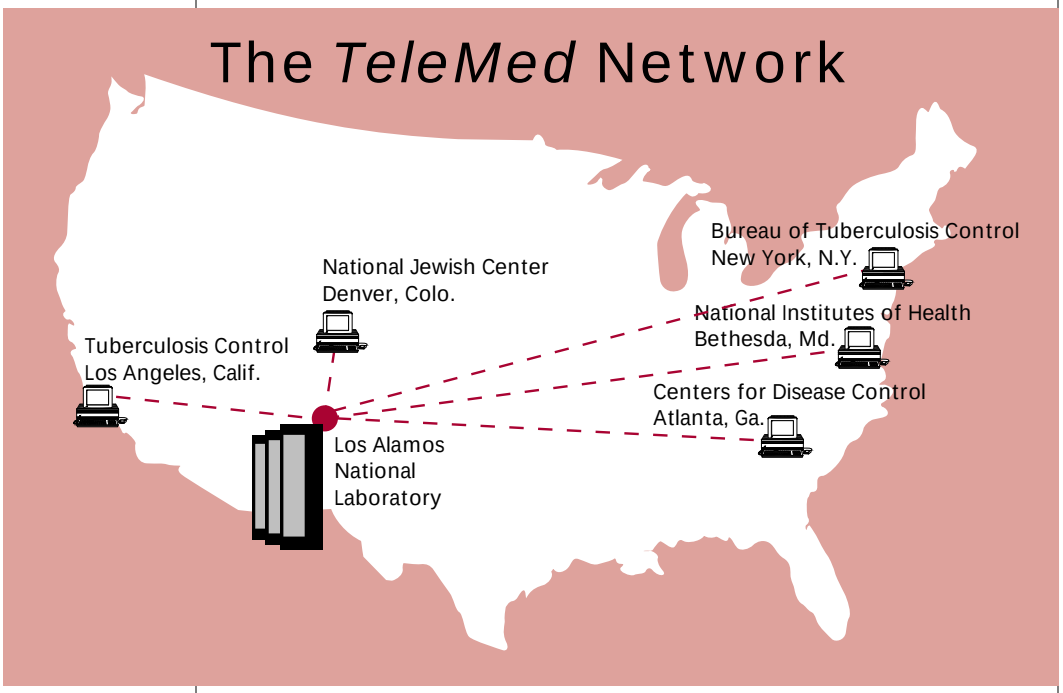
At present, physicians at the National Jewish Center for Immunology and Respiratory Medicine must obtain voluminous patient records from many different locations to review treatment histories and successes for multi-drug-resistant tuberculosis and other complex respiratory diseases. For patients with chronic lung diseases, the records may be several feet thick and contain as many as 200 X-ray images. The entire process can take hours of reading and review.

The difficulty physicians have in gathering and studying poorly organized patient information to prescribe effective treatment is a chronic condition in itself, according to Dr. John Newell, director of radiology at the NJC.

The Centers for Disease Control and Prevention report an increase in outbreaks of multi-drug-resistant tuberculosis with high fatality rates. Part of the reason for the increase, according to the National Institutes of Health, includes delayed diagnosis and ineffective treatment resulting in prolonged infections that become resistant to conventional drug therapy.

To speed identification of successful tuberculosis treatments, Los Alamos researchers are using supercomputers such as the Silicon Graphics Inc. Challenge XL and the Cray Research Inc. T3D to drive a radiographic records repository and telecollaboration system for the NJC and eventually other sites such as the NIH and the CDC.

Medical personnel from other organizations can access the power of the Los Alamos supercomputers through the TeleMed system. ↓



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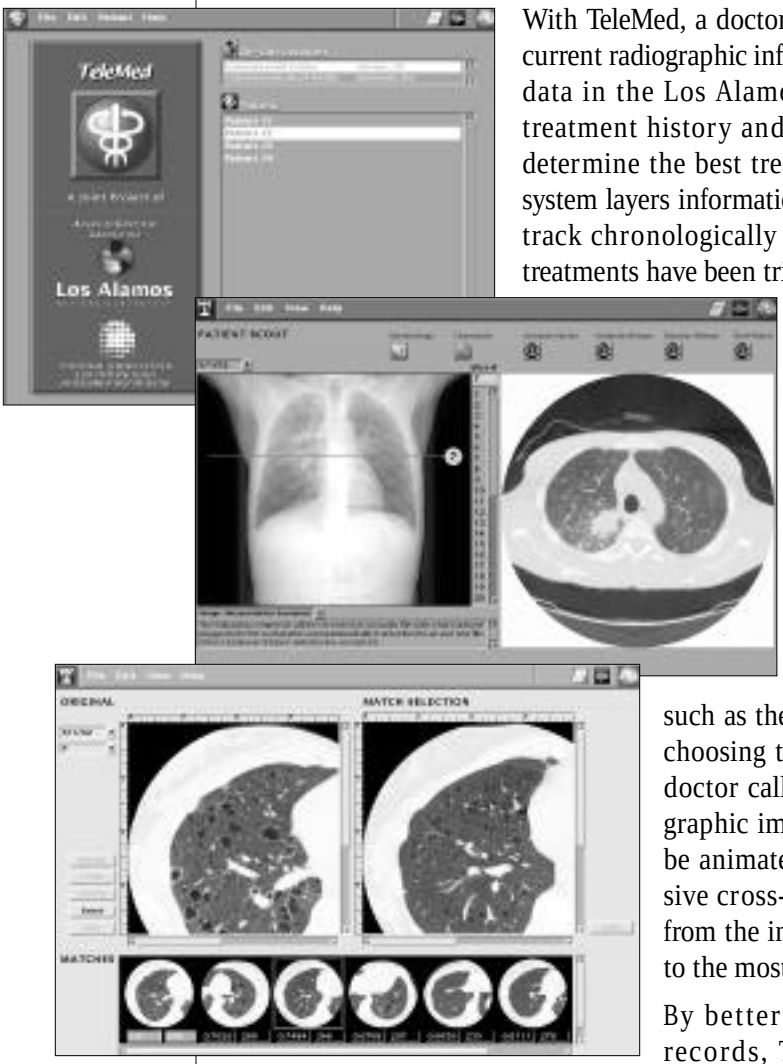
The physicians at the NJC access the TeleMed database using their desktop computers and a user-friendly, icon-based software system. With the click of a mouse button, the physician chooses a patient record from a list of patients displayed on the screen. Following that choice, the computer screen displays several icons for patient history, drug therapy, bacteriology, computed tomography or CT scans, and reports.




With TeleMed, a doctor can match a patient's current radiographic information with archival data in the Los Alamos repository, review treatment history and successes, and then determine the best treatment. The TeleMed system layers information so that doctors can track chronologically what medications or treatments have been tried and worked.

The patient's computer record is empty until populated by requests for information. For example, when the doctor clicks on the "drug therapy" icon, the TeleMed system harvests data from all appropriate sites, such as the NIH or the CDC. By choosing the "images" icon, the doctor calls up pertinent radiographic images. The images can be animated to show a progressive cross-section of the lungs, from the initial diagnostic X-rays to the most recent images.

By better organizing patient records, TeleMed allows the doctors to focus on treatments, resulting in lower costs and better patient care. For example, a doctor can arrest a tuberculosis case before it becomes drug-resistant for about $10,000. If a patient's tuberculosis becomes drug-resistant, treatment may cost up to $200,000.

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With the click of a mouse button, a physician working in a hospital or clinic can use TeleMed to access radiographic information from a national repository located at Los Alamos.

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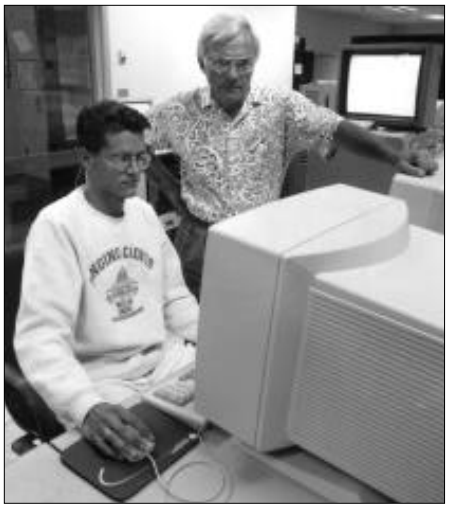

Los Alamos researcher Dick Phillips (standing) and summer student Kevin Gunn use the TeleMed system to call up lung images.

The radiographic data housed in the Los Alamos supercomputers is obtained either directly from a digital CT system or by scanning X-ray films. For now, Laboratory personnel input the records into the database. In the future, medical personnel will be able to enter the data from their place of work.

Medical personnel also can access the power of Los Alamos' supercomputers through TeleMed. The supercomputers will search the repository of radiographic images to find all those exhibiting certain specified features.

With the aid of a supercomputer, target images can be found in about 5 seconds. By comparison, it takes more than 75 seconds to perform the same search on a high-performance workstation. The researchers believe they can reduce the 5-second search to less than a second by exploiting the massively parallel architecture of Los Alamos' supercomputers.

Los Alamos plans to make TeleMed available to other tuberculosis programs in the United States, including the New York Bureau of Tuberculosis and the Los Angeles Department of Health Services.

TeleMed preserves patient confidentiality by requiring users to type in a series of passwords. As the system develops and more centers are brought online, researchers say patient confidentiality can be maintained.

If successful, the TeleMed project could eventually run as an application on the Internet, linking major hospitals with research, medical, and government institutions such as the CDC and the NIH.

TeleMed is part of a larger Los Alamos project called Sunrise, a prototype of a national information infrastructure development program. The object of Sunrise is to tie together computer technologies such as networking, distributed computing, security, multi-media, and data mining with specific applications.

CONTACT: RICHARD PHILLIPS
NETWORK ENGINEERING
(505) 665-1343

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# LOS ALAMOS AND INDUSTRY

## COOPERATIVE RESEARCH AND DEVELOPMENT AGREEMENTS

**CRADA**
Mini-Mitter Co.

Los Alamos and the Mini-Mitter Co. of Sunriver, Ore., will develop and commercialize the Telemetric Heat Stress Monitor to enhance the safety and efficiency of workers wearing chemical protective clothing. Hazardous-materials workers and firefighters wear clothing that protects them from external hazards, but the sealed environment of a protective suit makes the wearer susceptible to heat stress. Until now, the potential for heat stress had been determined primarily by environmental monitoring, which is ineffective in clothing that restricts air exchange. With the new system, workers will carry small monitors that telemeter their body temperatures and heart rates to a receiving station in a safe area up to a quarter mile away.

**CRADA**
Jasco Tools

Los Alamos and Jasco Tools of Rochester, N.Y., will evaluate the potential use of ion implantation for improving the performance and lifetime of tooling used in manufacturing. The automotive, computer, aerospace, and electronic industries require tools that have long useful lifetimes. Jasco has identified steels for evaluation because of their widespread use in the tooling industry. Los Alamos scientists will design, process, analyze, and evaluate ion implantation technology for the development of surface treatments for materials. The collaboration will investigate chemical composition and microstructure, and hardness, friction coefficient, and wear properties of tool materials.

**CRADA**
American Superconductor Corp.

Los Alamos and American Superconductor Corp. of Westborough, Mass., will develop high-temperature superconducting wires. Researchers will investigate methods to refine powder-in-tube high-temperature wire manufacturing targeted for use in commercial electric power applications. The project has already improved the performance of wires produced in American Superconductor's pilot manufacturing line and presents the commercialization process for high-temperature superconductor technology. Much of the basis of this agreement is in support of a larger collaboration — the Wire Development Group, which involves researchers from Oak Ridge and Argonne national laboratories, the University of Wisconsin, and the National Institute of Standards and Technology.

For more information about these and other cooperative research and development agreements, contact the Industrial Partnership Office at (505) 665-9090.

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## BRIEFLY ...

Theoretical physicist Michael Martin Nieto recently received Germany's Humboldt Research Award for senior U.S. scientists. Nieto was honored by the Alexander von Humboldt Foundation for his contributions to theoretical physics in research and teaching. His teaching assignments have included Purdue and Kyoto (Japan) universities and the University of California at Santa Barbara. The award entitles Nieto to conduct research for up to one year at the German institute of his choice. Nieto has chosen to work at the University of Ulm.

Jim Toevs is the Laboratory's new project leader for Nuclear Materials Disposition. Toevs has oversight of Los Alamos' efforts for the control and disposition of surplus fissile material. Surplus fissile material is material that can be used to make nuclear weapons and has been declared excess or surplus — no longer needed for the stockpile. It includes material, primarily plutonium, from dismantled weapons as well as residues created during plutonium processing. Toevs' project is part of the national Department of Energy Fissile Materials Disposition Program.



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