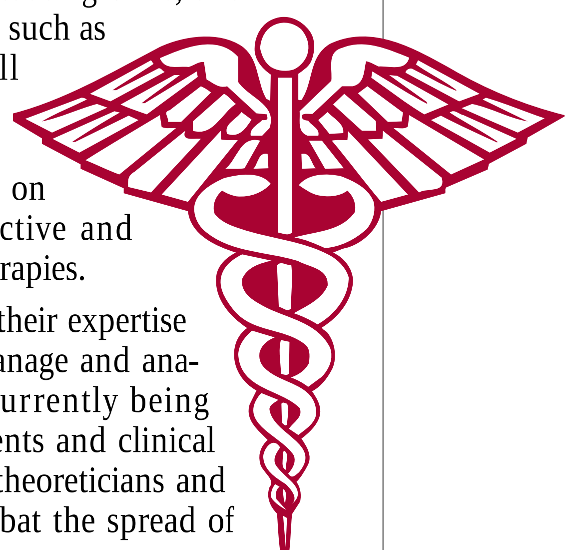
LOS ALAMOS NATIONAL LABORATORY
WHERE SCIENCE MAKES A DIFFERENCE

DATELINE
LOS ALAMOS

MOLECULAR MEDICINE FOR THE 21ST CENTURY

ADVANCED DATA ANALYSIS AND THEORETICAL MODELS SPEED DEVELOPMENT OF NEW DRUGS AND VACCINES

In the next century, "biological warfare" against new viruses such as HIV, the AIDS-causing virus, and new deadly strains of old menaces such as tuberculosis may supersede all other forms of combat. The ability to fight off these major health threats will depend largely on scientists' ability to design effective and inexpensive vaccines and drug therapies.



Los Alamos researchers are using their expertise in theory and computation to manage and analyze the flood of information currently being generated in laboratory experiments and clinical trials. Their efforts will aid both theoreticians and experimentalists working to combat the spread of contagious diseases.

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The extraordinarily rapid spread of HIV and the emergence of persistent drug-resistant strains of tuberculosis, cholera, and other infectious diseases has resulted in a wealth of information from experimental and clinical studies; so much information, in fact, that new approaches to treating infectious diseases are lagging behind the successful acquisition, processing, and publishing of scientific data.

By combining the Laboratory's supercomputing power with advanced techniques in data analysis, Los Alamos researchers can help the medical community select the most promising vaccines and drug treatments, rapidly evaluate changes in pathogens that begin to display drug resistance, and identify

← A teacher instructs patients at the Hazelwood Tuberculosis Hospital in Louisville, Ky. Surgical masks prevent the spread of germs. TB germs are transmitted through coughing, sneezing, or even talking. In the United States, 15 million people are infected with tuberculosis and more than 26,000 new active cases of TB are reported each year. Multi-drug-resistant TB, which counts for one-third of all cases in some areas of this country, will cost the United States $2 billion this decade. TB is also a leading secondary infection of AIDS patients.

Photo courtesy of AP/Wide World Photos

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new ways of overcoming an emerging resistance. The intended result: scientists run up fewer blind alleys looking for cures.

To close the gap, Los Alamos researchers are collaborating with pharmaceutical companies and other laboratories to collect, interpret, and integrate the vast collections of available data into a coherent structure.

Los Alamos has a long tradition of investigating health-related topics. This tradition stems from the Laboratory's earliest days when the effects of radiation on workers' health were first studied. As a consequence of these concerns, Los Alamos launched a research program to understand the health effects of exposure to different types of radiation and chemicals. These substances can adversely affect health by damaging cell DNA, which can lead to tumors and cancers.

➔ This 1954 photo depicts two polio patents in iron lungs being transported to a treatment center. An attenuated polio vaccine was first produced by Jonas Salk in 1955, followed by a live oral vaccine in 1961 by Albert Sabin. Vaccines to protect against polio outbreaks were produced after several decades of scientific research. Los Alamos researchers are developing mathematical and computational tools that will help speed the development of effective and inexpensive vaccines and drug therapies for infectious diseases. Photo courtesy of AP/Wide World Photos

A number of individual research projects have evolved from the Laboratory's efforts to understand the mechanisms that alter DNA, including the GenBank, a database of human DNA sequences; the flow cytometer, a laboratory tool capable of sorting individual DNA molecules; and the Center for Human Genome Studies, which was established to help decode the DNA of all 22 pairs of human chromosomes plus the X and Y sex chromosomes. The field of molecular medicine builds on Los Alamos' extensive experience in gene research.

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MOLECULAR DIVERSITY

In the past, drugs were developed primarily by exploiting the innate disease-fighting properties of plant and animal tissue. This method produced many effective drug therapies, but researchers fighting on the front lines of the AIDS pandemic know that traditional drug treatments are too sluggish to hobble HIV's swift ability to replicate and mutate inside the body.

Scientists still look to nature for cures, but the development of new vaccines and drug therapies relies increasingly on a relatively new discipline known as molecular medicine.

At Los Alamos, the computational aspects of molecular medicine are under development. This kind of medical research uses computers to design drugs and vaccines and measure their effectiveness, or "fitness," when pitted against pathogens in a virtual world known as a "rugged landscape."

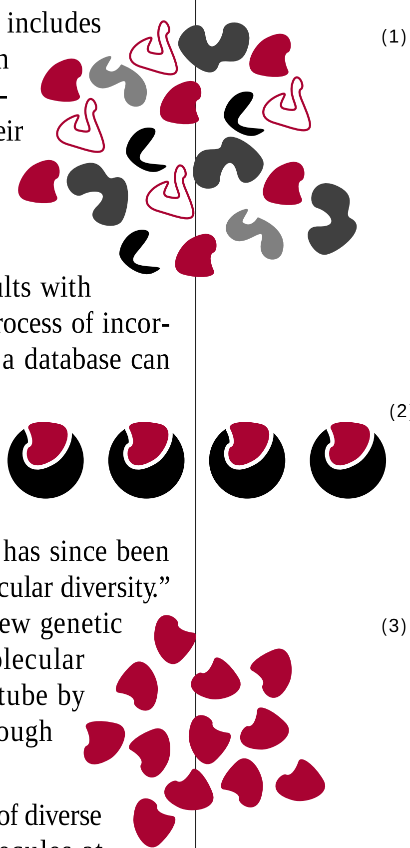
Los Alamos researchers are involved in a consortium that includes academic institutions and commercial drug and biotech companies to develop computer models capable of analyzing molecular sequence data. Modeling drugs and their interactions with pathogens in this fashion will suggest to experimentalists what drugs to develop by predicting their ability to combat pathogens.

The experimentalists, in turn, share their research results with theoreticians and computer scientists, who are in the process of incorporating the information into a central database. Such a database can provide a forum where theoreticists and experimentalists can exchange results and information.

Some of the computer modeling tools being used at Los Alamos were developed initially to analyze rapidly mutating viruses such as HIV. The modeling technique has since been expanded to the new and highly promising field of "molecular diversity." Rather than relying on nature to generate and select new genetic variations, this field — sometimes called applied molecular evolution — lets scientists control evolution in a test tube by creating an environment in which molecules evolve through artificial selection.

The idea behind molecular diversity is to generate billions of diverse pieces of DNA, RNA, proteins, or other organic molecules at

Molecular evolution lets scientists control evolution in a test tube by creating an environment in which molecules evolve through artificial selection. For example, a diverse pool of molecules (1) is mixed with possible antibodies (2), which then make copies of the molecules that fit (3).



random, then see which do best at, for instance, fitting into a receptor on the protein envelope that encapsulates the virus' genetic material. (The HIV protein envelope continues to offer the principal target for a successful vaccine.) Top candidates identified in this manner are reproduced with mutations, and the screening process is repeated. This is an accelerated laboratory version of evolution through natural selection that allows researchers to develop and test huge numbers of variants in a matter of hours. The data output of molecular diversity experiments is tremendous. Los Alamos is currently developing databases and analysis algorithms to handle this flood of data.

➔ Dan Kinder of GlaxoWellcome uses a robot to synthesize chemical libraries. Los Alamos researchers are working with commercial pharmaceutical and biotech companies and academic institutions to develop theoretical models of drugs and their interactions with pathogens. Such models save valuable time and resources by predicting how a drug will combat a particular pathogen. Photo courtesy of GlaxoWellcome

PATTERNS IN PATHOGENS

Over the last decade, new and advanced laboratory techniques such as polymerase chain reaction and automated sequencing of molecules have provided detailed information about genetic variation in pathogens such as HIV and HPV, the latter being the human papilloma virus responsible for diseases ranging from harmless skin warts to lethal cancers.

A database initiated in 1986 at Los Alamos includes genetic sequence information on HIV as the sequences are identified by researchers around the globe. Information contained in the HIV Sequence Database is used each year by more than a thousand researchers worldwide.

Computational analysis of the molecular sequence data has resulted in specific suggestions for improved vaccines for a dominant strain of HIV.

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A child suffering from cholera waits with his mother in a Lima, Peru, hospital for treatment. By the time this photo was taken in April 1991, the cholera epidemic in Peru had claimed more than 1,000 lives. New outbreaks of cholera appear when hygiene practices are inadequate and food and water supplies become contaminated. Photo courtesy of AP/Wide World Photos

The suggestions have been incorporated into new vaccines presently undergoing development and testing by collaborating pharmaceutical companies. The researchers have identified eight different families, or subtypes, of the dominant form of the HIV virus, providing valuable insight into how rapidly the virus changes as it spreads through the population.

The World Health Organization's global program on AIDS selected the Los Alamos researchers to advise them on the molecular characterization of AIDS viruses in Uganda, Rwanda, Thailand, and Brazil, the four countries in which WHO is undertaking preliminary vaccine trials.

The Centers for Disease Control requested information from Los Alamos on HIV molecular sequences while investigating a Florida dentist with AIDS who allegedly infected five of his patients. The CDC also turned to Los Alamos for help tracking transmission of immunodeficiency viruses of apes and monkeys to lab workers handling animal viruses.

Los Alamos recently initiated a similar database for the human papilloma virus. HPV is the leading sexually transmitted disease in the world. Cervical cancer, caused by a few of the 75 or more known types of HPV, is a leading cause of cancer-related deaths in women in the world.

IMMUNE SYSTEM-PATHOGEN INTERACTION

Models of the interaction of the immune system with pathogens have been developed at Los Alamos and used in collaborative projects to evaluate potential treatments for HIV. The goal of these models is to help scientists devise novel ways of manipulating the immune system for commercial applications.

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Los Alamos researchers are collaborating with scientists at Lawrence Livermore National Laboratory and the University of California at San Francisco to examine the effectiveness of localized heat treatments on patients' lymph nodes as a means of inactivating HIV. The researchers are refining their models to take into consideration the special conditions of lymph nodes and other reservoirs of HIV.

Another study builds on scientists' recent discovery that some kinds of ribonucleic acid, or RNA, can act as enzymes and break up other RNA molecules into short segments incapable of replicating. Los Alamos researchers have used mathematical models to examine a treatment that packages these RNA "scissors" in a virus capable of infecting HIV-infected cells. Their models evaluated a blueprint for the virus, which the National Institutes of Health is developing.

➔ By combining the Laboratory's supercomputing power with advanced techniques in data analysis, Los Alamos researchers Alan Perelson (left), Alan Lapedes (center), and Gerald Myers are helping the medical community select the most promising vaccines and drug treatments for new deadly viruses and tougher strains of old infectious diseases.

In the course of modeling and assessing treatments for HIV and other pathogens, the researchers gained a new understanding of how the body battles HIV. A report of this study appeared in the January 1995 issue of *Nature*. Using clinical data obtained from New York University's Aaron Diamond AIDS Research Center, the researchers for the first time quantitatively documented HIV's tremendous replication rate in the body.

The study also demonstrated that the immune systems of AIDS patients are continuously churning out armies of T-cells, but HIV's burgeoning population ultimately overwhelms the capacity of the body's immune system. (See related article in the March 1995 issue of *Dateline: Los Alamos*.)

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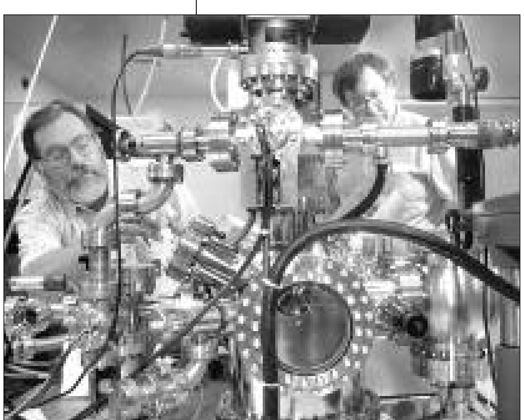
NEW COMPUTER DATA STORAGE MEDIA IS VIRTUALLY INDESTRUCTIBLE

LOS ALAMOS-DEVELOPED TECHNOLOGY CAN STORE DATA FOR THOUSANDS OF YEARS

Step on it, it won't break. Try to set it on fire, it won't burn. Place a magnet next to it, it won't erase. What is it? It's HD-ROM, or High-Density Read-Only Memory, developed at Los Alamos. This new information-storage technology is more durable and more reliable than CD-ROM, or Compact Disc Read-Only Memory, and has the capacity to store two complete sets of Encyclopædia Britannica on a steel pin less than 3 inches long.

HD-ROM's main purpose is to store archival data, but it also can store high-density data in binary (digital), alphanumeric (human-readable), and graphic formats. Not only can various types of data be stored on HD-ROM, but data can be stored at different densities.



← Researchers Bruce Lamartine (left) and Roger Stutz make adjustments to the ion-beam micromill. This machine writes data on HD-ROM media.

This feature makes it possible to store textual and graphical information together — a feature no other media can perform. Conventional media require that graphical information and text be stored on separate disks. And, unlike existing materials, in HD-ROM, the data is written directly on the media. Because of its durability, the HD-ROM will outlast the computer system the data was processed on. This eliminates the need to transfer data to new physical media when the original wears out.

HD-ROM is a component of a system that includes an ion-beam micromill, or data writer, and a force-tunneling microscope, which is a commercial system for reading data. Etching information directly on the media speeds the rate at which the data can be read. The writing process involves an ultrahigh vacuum environment that allows for high density and clean etching of information. The vacuum eliminates the

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smearing that sometimes occurs when data is written on media at high pressures.

Bigger doesn't necessarily mean better. It takes 12,000 computer floppy disks to store the information that fits on the tiny steel pin, seen at the center of the disk. The pin can store two complete sets of the Encyclopædia Britannica.

Today's information storage media are highly perishable. Most of their components come from magnetic materials that are sensitive to solvents and other magnetic materials.

Researchers would prefer to use materials like steel, iridium, and silicon because of their ability to withstand mishandling and natural degradation. Media constructed with these materials are so durable that exposure to solvents or other magnetic materials has no effect on the encoded data. Solvents will only clean steel and because the HD-ROM is non-magnetic, materials with magnetic properties won't damage or erase data. Records will last for hundreds, even thousands, of years.

Existing information-storage media have another drawback. Interpreting computer data visually from media such as magnetic tape and optical disks is as difficult as interpreting ancient Egyptian hieroglyphs without the Rosetta Stone.

CD-ROM and floppy disks are encoded with a bit-stream of "ones" and "zeroes" that represent information. This is known as binary data. The average person can't tell what those ones and zeroes mean. So, computers need a bit-stream interpreter to translate whether a stream of ones and zeroes is a number, a portion of a picture, or the sound of music.

HD-ROM does not require a bit-stream interpreter for alphanumeric and graphical formats because visually apparent characters are recovered directly. For binary data, HD-ROM describes in human-readable format the instructions needed for the interpreter to read the data.

HD-ROM has potential applications in areas such as bank transaction records, surveillance mapping, seismic records, and even audio and video cassette masters. The researchers estimate the manufacturing costs for HD-ROMs will be comparable to the manufacturing costs of CD-ROMs.

Los Alamos is actively seeking an industrial partner to turn HD-ROM into a marketable product. Patents on HD-ROM and the ion-beam micromill are pending.

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LOS ALAMOS DEVELOPS NEW METALLIC MEMBRANE FOR FILTERING HYDROGEN

THIN FOIL MEMBRANE OUTPERFORMS OTHER FILTERS AVAILABLE TO INDUSTRY

Pure hydrogen — and nothing else — passes through a new metallic membrane invented by Los Alamos researchers.

The new filter may find applications in a broad range of industries because it can remove or supply pure hydrogen faster and less expensively than current systems. For example, it could advance the development of hydrogen fuel cells, a technology intended to replace gasoline-burning engines. One drawback to the fuel-cell technology is that impurities quickly poison the cells if pure hydrogen is not used. The thin metallic membrane developed at Los Alamos allows only hydrogen to pass through it and is economical enough to be practical for a fuel cell.

In another application, the metallic membrane could be used to speed the dehydrogenation process used in creating numerous plastics and polymers, while capturing a supply of pure hydrogen to power the factory.

Los Alamos researcher Nathaniel Peachey makes adjustments to an apparatus used for testing a new metallic membrane.

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The Los Alamos membrane, which operates even better at high temperatures (above 300 degrees Celsius) and increased pressure than at room temperature and atmospheric pressure, attractive economically because unlike existing filters it can be produced in large sheets, or rolls.

The membrane resembles common aluminum foil. The Los Alamos researchers produced the membrane with the readily available metals tantalum and palladium. Tantalum is a relatively strong and inexpensive metal with the special property that hydrogen atoms can pass easily through it, so this metal is used as the structural support of the membrane.

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The thin foil membrane allows pure hydrogen, and nothing else, to filter through. Researchers applied Los Alamos' expertise in thin film fabrication to produce a fused sandwich of the readily available metals tantalum and palladium.

Tantalum foil about 13 micrometers thick is cleaned in a vacuum chamber by bombarding it with argon ions, a conventional technology. Next, without breaking the vacuum, both sides of the cleaned foil are coated with a 1-micrometer-thick layer of pure palladium. The resulting fused metallic sandwich eliminates much of the cracking and oxidation problems common to other membranes.

The key to the filter's success is the way hydrogen molecules respond to the metal sandwich. A hydrogen molecule binds to the palladium surface and breaks into two individual atoms. The atoms then pass through the tantalum much faster than they would through just a palladium membrane. When the atoms reach the outer surface, another thin palladium layer recombines the atoms back into a hydrogen molecule. The filtered product is pure hydrogen in high volume. To encourage hydrogen's passage through the filter, the researchers nudge the gas onto the filter and apply suction on the other side to pull purified hydrogen off the filter.

The researchers have filed a patent on this new technology.

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BRIEFLY ...

NEW MEXICO COMMUNITY COLLEGES SEND FACULTY AND STUDENTS TO SUMMER SCHOOL AT LOS ALAMOS. Seven faculty members and students from community colleges in Carlsbad, Española, Farmington, and Las Vegas recently completed eight weeks of research in advanced manufacturing at Los Alamos. Their research projects were tailored to give them knowledge that will help their respective communities develop new science facilities and programs. A student from New Mexico State University in Carlsbad conducted surveys and interviews with Carlsbad-area businesses on the development of a planned Advanced Manufacturing and Innovative Training Center that will identify new markets and projects as well as provide training programs. Two representatives from Northern New Mexico Community College in Española gained knowledge to advance the development of a new microelectronics academic program. Two representatives from San Juan College in Farmington have returned to their campus with hands-on experience in precise machining that will enhance instruction in the field. And two representatives from Luna Vocational Technical Institute in Las Vegas designed a computer-integrated manufacturing laboratory that will be housed in a refurbished building near the Institute's main campus. CONTACT: ABAD SANDOVAL, (505) 667-1230, E-MAIL: abad@lanl.gov

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