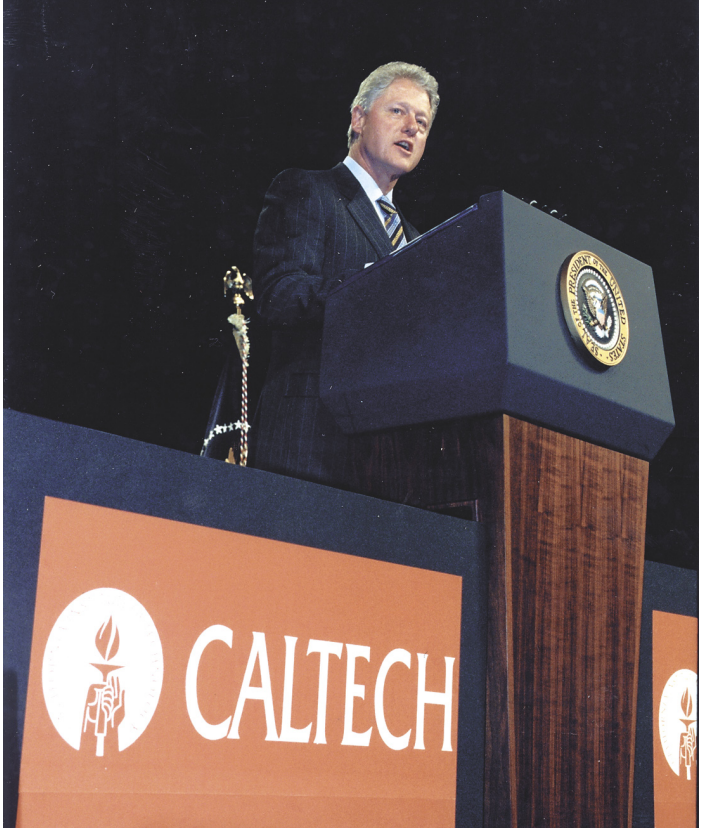

Bill Clinton speaks from the Beckman Auditorium stage.

The President Comes to Town

Above: Clinton tries out one of the set of Liquidmetal golf clubs presented to him by Caltech President David Baltimore. They're actually made of metallic glass, a stronger and more flexible noncrystalline metal developed by William Johnson, the Mettler Professor of Engineering and Applied Science.

Right: The President mingles with a crowd of students after his talk.

President Bill Clinton chose Caltech as the site to unveil his science and technology budget for the 2001 fiscal year and announced to a packed Beckman Auditorium on January 21 that he was proposing a $2.8 billion increase.

His proposed budget includes a $675 million increase for the National Science Foundation—double the largest increase in NSF's history—and $1 billion more for biomedical research at the National Institutes of Health. In addition, two specific fields were singled out for generous funding: information technology research, for which $600 million is earmarked, and a new $497 million National Nanotechnology Initiative. Clinton, standing in front of a backdrop of the western hemisphere drawn in gold atoms (enlarged for the occasion), noted in his speech that Richard Feynman had first prophesied the field of nanotechnology at Caltech ("There's Plenty of Room at the Bottom," *E&S*, February 1960).

Clinton praised a number of Caltech's accomplishments and said that the government has "not done a good job of explaining why we need large investments in science; we have to explain why science is important and how it affects people's lives." Research at universities is "a top priority," Clinton said, as is the next generation of scientists. He stressed the need to recruit more minority students into science and technology and to help them graduate, and he reiterated his support for student loans and tax deductions for college tuition, which he had announced the previous day. And the President received a round of applause when he noted the benefits we have gained from scientists born in other countries; "we should continue to welcome them to our shores."

In conclusion, Clinton told the members of the audience, "You have the power to put science and technology to work," but he urged them to "keep human values at the center."

Then, instead of being whisked away by the Secret Service, the President left the stage and, to the strains of Elton John's "Rocket Man," joined the delighted Caltech crowd, shaking hands and posing for pictures for more than half an hour. □

Aging and Mitochondrial DNA

Certain effects of aging could be caused by mutations in the DNA molecules of the energy-producing engines of cells known as mitochondria, according to new research from Caltech and the University of Milan.

The study describes the results of skin-cell biopsies of about 30 individuals in a variety of age groups. The study concludes that damage to mitochondrial DNA dramatically increases around the age of 65.

"It's not a magic number, but we see a clear trend," says Giuseppe Attardi, the Grace C. Steele Professor of Molecular Biology and leader of the team authoring the paper.

Attardi and his colleagues focused their efforts on the small structures in mitochondria. Every cell can have tens to hundreds of these structures, which play an important metabolic role in the energy production that allows the cell to do its work.

Each of the mitochondria has about 10 to 20 molecules of DNA, which means that a single cell can have hundreds or thousands of mitochondrial DNA molecules.

But mitochondrial DNA is known to be susceptible to mutations over the course of a lifetime. These mutations can be due to oxidative damage, some enzyme malfunction, or even the cell's own efforts to repair itself. But prior to the new study, molecular biologists had difficulty detecting aging-related mutations.

Over a period of about five years, Attardi and his colleagues developed a technique for detecting aging-related mutations in the main control region of mitochondrial DNA. This provided a very reliable method for determining the percentage of mitochondrial DNA molecules in a cell that had actually undergone mutations.

With this technique, they then studied tissue samples provided by the National Institutes of Health (NIH) and the University of Milan from skin biopsies. These biopsies came from individuals ranging from a 20-week-old fetus to a 101-year-old subject, which allowed the researchers to determine the prevalence of mutations in different age groups.

The results showed virtually no aging-related mutations for any of the subjects under the age of 65. But a dozen or so individuals above the age of 65 showed a dramatic increase in mutations. And not only did the rate of mutations sharply increase with age, but individuals also showed a sharp increase in mutations if they passed the age of 65 between biopsies.

Overall, the researchers found that up to 50 percent of the mitochondrial DNA molecules had been mutated in subjects 65 or over.

Attardi says future study will be needed to ascertain the precise effects of the mutations and the relationship to the known characteristics of aging. In addition, the researchers would like to know how the original mutation "amplifies," or is established in thousands of other molecules.

Also, the precise mechanism of the mutations is not known at this time. And finally, the study was done only on skin cells, although Attardi says the effect may possibly be seen in other cells of the human body.

In addition to Attardi, the other authors are Yuichi Michikawa, a senior research fellow in biology at Caltech; and Franca Mazzucchelli, Nereo Bresolin, and Guglielmo Scarlato, all of the University of Milan. □ — *RT*

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Heart Drug Inhibits Melanoma Growth

Professor of Biology Paul Patterson and researchers Ronit Lahav and Garrett Heffner have discovered that one type of drug used for human heart disease can inhibit the growth of skin cancer cells.

The drug, known as BQ788, is proving effective in suppressing skin cancer in mice, and drugs of this type could have potential for ovarian and prostate tumors as well. The Caltech team reports that the drug can stop melanoma tumor growth and even reduce tumors in some cases.

Further, the drug seems to be effective both as a direct treatment of the tumor and when injected systemically into the animal. The latter result is particularly promising as it has the potential for also suppressing metastasis, or the spread of tumors to other organs, says Patterson.

"If you went to the doctor with a tumor on the skin, he would take it out immediately," says Patterson. "So the first line of treatment is to surgically excise the tumor, and if it's a superficial tumor, you essentially have a complete cure.

"But the worry is when the

"We think this drug could turn out to be an effective way to stop cancer cells from spreading, or at least stop their growth if they have already spread."

tumor has penetrated more deeply and already metastasized," he says. "We think this drug could turn out to be an effective way to stop cancer cells from spreading, or at least stop their growth if they have already spread."

The strategy is based on the targeting of "growth factors," or proteins that cells use to stimulate their growth. The cancerous state represents a reversal of healthy, mature cells to a state similar to that of embryonic cells. In other words, cancerous cells tend to multiply rapidly, just as cells do in a developing embryo.

Lahav, the lead author on the paper, reasoned that melanoma cancer cells perhaps use a growth factor similar to that employed by their precursor cells in the embryo. She showed that such a growth factor, called endothelin, acts on the embryonic cells, and is also made by the cancer cells. By serendipity, the heart drug BQ788 is an antagonist for the endothelin receptor B. Thus, BQ788 is a substance that disrupts the receptor from performing its function in the cell.

Lahav found that this drug can stop human melanoma cell growth when introduced into cell cultures. In fact, the drug not only makes the cells stop dividing, but it can also kill such cells.

When the drug was given to mice with tumors, tumor growth slowed dramatically, and in some cases even regressed.

"It works whether you inject it into the tumor or into the body cavity," Patterson says. "In about half the mice, the tumors actually shrank."

Patterson says there is reason to think this type of drug could also work on certain other cancers (ovarian, prostate) where runaway cell growth may also be controlled by the same growth factor, endothelin.

Ronit Lahav is a postdoctoral scholar from Israel, and Garrett Heffner is a Caltech sophomore who participated in this research the summer after graduating from high school. □ —*RT*

Log onto the new Web site @Caltech at http://atcaltech.caltech.edu for daily information about campus news and events. There's a campuswide calendar listing everything from public and academic events to student-club activities, and a Web theater will bring you broadcasts of campus events, such as President Clinton's recent speech. You can read articles from *Caltech News, On Campus,* and even *Engineering & Science*—if you'd rather read it on a screen than on paper.

Worm Love and Kidney Disease

For a male nematode, the LOV-1 gene couldn't be more aptly named. The millimeter-long roundworm, if its LOV-1 gene is functioning properly, has the eagerness to mate and the instincts to perform successfully.

But if the LOV-1 gene is disabled, the male nematode is truly clueless. The fact that "LOV" is an acronym for "location of vulva" pretty much says it all.

While there is no such single gene controlling sexual interest and instinct in humans, Paul Sternberg, professor of biology and Howard Hughes Medical Institute investigator, and postdoc Maureen Barr, who recently identified the LOV-1 gene, say there is a similar human gene involved in a type of kidney disease. The LOV-1 gene has a sensory role in nematodes, but the human homolog (or counterpart) is PKD1, or polycystic kidney disease gene 1.

In other words, a male nematode that has this particular gene intact is able and willing to mate, while a human with the gene intact is disease-free. But if the genes are respectively knocked out, the nematode is sexually dysfunctional and the human is prone to autosomal dominant polycystic kidney disease, a serious disease that afflicts about one in 1,000 people and may ultimately result in renal failure.

"This is a surprise," says Sternberg. "We can only speculate on what the connection might be."

PKD1 and a second gene, PKD2, account for about 95 percent of all cases of autosomal dominant polycystic kidney disease. These genes cause the human body to produce polycystin 1 and polycystin 2, which are thought to work somehow in concert at the molecular level.

In an analogous manner, the LOV-1 gene also seems to

work in concert with the PKD-2 gene, which in nematodes is the counterpart of the PKD2 gene in humans. The fact that the genes in both humans and nematodes seem to work in pairs actually strengthens the likelihood that there is some underlying molecular relationship, Sternberg says.

Much of the lab work leading to this discovery was done by Barr, who painstakingly watched in a microscope for male nematodes who were not successfully mating.

Barr then singled out the dysfunctional males and used standard genetic screening techniques and DNA sequencing analysis to identify the LOV-1 gene, which when mutated, is responsible for the lack of mating behavior.

While the researchers are not clear on why a gene involved in mating behavior in one species would be involved in disease in another, they say there could be a couple of possible explanations.

For one thing, the connection between the human gene and the worm gene might be very basic. Perhaps the gene is involved in setting up polarity of human kidney cells and polarity of worm neurons that govern sexual behavior.

In the case of the worm, the LOV-1 might actually act as part of a sensory signaling pathway responding to the presence of a mating partner by altering the electrical properties of the specific nerve cell that senses the mate.

Or perhaps the underlying relationship has to do with cell structure, Sternberg says. In this case, the LOV-1 protein might function as a molecular scaffold for other molecules, or promote the assembly of many molecules to create structures such as the sensory neuronal cilia.

Sternberg and Barr say the scientific goal of the study was to investigate ways in which genes influence behavior. But the findings could also serendipitously point to new avenues for research on autosomal dominant polycystic kidney disease.

"This is a mystery disease, so it could be that renal failure is just the first defect in a disease with broader manifestations," Sternberg says. In that case, improved knowledge at the molecular level could lead to different approaches in identifying treatments or even a cure.

"Here's a new way to study the basic mechanism," Sternberg says. □ —*RT*

Right: During the November 12 dedication ceremony of the Livingston, Louisiana, site of the Laser Interferometer Gravitational-Wave Observatory, Mark Coles (right), head of the Livingston observatory, explains what goes on in the laser/vacuum equipment area. Among the guests are Caltech President David Baltimore (next to Coles) and Rita Colwell (left, foreground), director of the National Science Foundation. The ceremony celebrated completion of construction. The two LIGO detectors (the other one is in Hanford, Washington) should be up and running together in 2001.

Watson Lectures - 2000

February 9: Sampling the Universe — *Edward Stone*, director of JPL, vice president, Morrisroe Professor of Physics

March 1: Caltech: An Entrepreneurial Leader — *Kenneth Pickar*, Johnson Visiting Professor of Mechanical Engineering

April 12: Acts of God, Acts of Man: How Humans Make Natural Hazards into Disasters — *Kerry Sieh*, professor of geology

May 3: Images of the Early Universe — *Andrew Lange*, professor of physics

May 17: A Different View of the DNA Double Helix: A Conduit for Charge Transport — *Jacqueline Barton*, Hanisch Memorial Professor and professor of chemistry

October 4: Combined Value Markets — *John Ledyard*, division chair, professor of economics and social sciences

October 18: The Evolution of Big Brains — *John Allman*, Hixon Professor of Psychobiology and professor of biology

November 1: The Keck Telescope at the Age of Five Years: The Early Childhood of a Scientific Giant — *Judith Cohen*, professor of astonomy

November 15: Memories of Caltech Past — *Judith Goodstein*, university archivist, registrar, faculty associate in history