Not too many decades ago, being diagnosed with diabetes amounted to a death sentence. Today, modern medicines, coupled with exercise and a careful diet, enable many people with the most common form of diabetes (type 2, also called late onset diabetes) to live longer and better.

But, as The New York Times series illustrates, today’s growing population of diabetics is not home free. The wear and tear of fluctuating blood sugar levels that are the hallmark of the disease can damage their bodies’ cells and tissues, setting the stage for heart attacks, strokes, blindness and kidney failure — diseases that can seriously impair, and

continued on page 2
even end, patients’ lives.

With more people expected to develop diabetes in coming years, many public health officials and physicians look to the Salk Institute and other leading basic research laboratories for the insights that could inspire new approaches to diabetes prevention and care.

At the Salk Institute, several faculty members conduct basic research to unravel the genes and molecules that play a role in, for example, stabilizing blood levels of glucose (sugar), the molecule that supplies our bodies with energy.

“Figuring out how to control glucose production in the liver is critical because many complications of diabetes, such as heart disease, kidney failure and blindness, can be reduced by maintaining a very tight control over blood sugar levels,” said Marc Montminy, M.D., a professor in the Salk Institute’s Clayton Foundation Laboratories for Peptide Biology.

Several years ago, Montminy and his lab team discovered an important genetic switch in our bodies’ delicate energy balance. Putting the brakes on the switch may lead to new therapies that keep blood glucose levels under control.

Glucose is one of the nutrients that surge through your blood stream after you eat a meal. Because a high blood glucose level is unhealthy, your pancreas releases insulin to instruct your body’s muscle and liver cells to squirrel away the glucose not needed immediately. The surplus fuels your body’s cells when you can’t eat — for example, when you are asleep.

But the bodies of people with type 2 diabetes turn a deaf ear to insulin’s urgent message. Normally, when energy stores run low, the pancreas releases the hormone glucagon into the blood stream. It not only tells cells to dip into their glucose reserves, hoarded in times of plenty, but also activates a whole complex network of signals and switches in the body’s cells.

Montminy discovered that turning on the genetic switch (called CREB), on which all other signals converge, revs up glucose production in the liver. In people with type 2 diabetes, however, very often the CREB switch is stuck in the “on” position. The liver, in response, churns out glucose throughout the day even when blood sugar levels are already high.

Also relevant to diabetes is the basic research of Ronald Evans, Ph.D., professor and director of Salk’s Gene Expression Laboratory. He probes the molecular connection between obesity and diabetes, and in particular, a family of genes that controls fat storage and burning.

Among the genes that he discovered is the molecular target of Actos and Avandia, which belong to the newest generation of anti-diabetic medications.

The drugs’ target, a molecule named PPAR gamma, regulates fat storage. When PPAR gamma is activated, it sensitizes muscle cells to insulin, lowering levels of circulating glucose. Its sibling, PPAR delta, controls the cells’ ability to burn fat. Evans believes that drugs that activate the PPAR delta pathway will combat and protect against diabetes. One such experimental drug is in phase II clinical trials to determine its safety and effectiveness in lowering liver production of sugar and fat. A drug that achieves this result should be helpful in treating heart disease.

Type 2 diabetes usually begins as insulin resistance and gradually develops into full-blown diabetes as we grow older. Andrew Dillin, Ph.D., assistant professor in the Molecular and...
Cell Biology Laboratory, discovered why: both diabetes and the aging process are regulated by the insulin-signaling pathway. Now, he is trying to manipulate this molecular pathway to influence the aging process independently from diseases associated with aging.

Reflecting the nature of basic research, new insights emerge unexpectedly, as was the case in a recent study by assistant professor Reuben Shaw, Ph.D., who just joined the Institute’s Molecular and Cell Biology Laboratory from Harvard Medical School. When he turned off Lkb, a gene that normally functions as a brake on cancer cells, the lab animals’ blood sugar levels shot through the roof. Because cancer cells are very active, they usually require more fuel to survive. So limiting their energy supply limits their growth. Shaw’s experiments, performed in collaboration with Montminy, revealed how Lkb controls the liver’s glucose production. The research also showed how metformin, a drug used to treat type 2 diabetes for nearly 50 years, amplifies insulin’s effects.

In contrast to people diagnosed with type 2 diabetes, those with type 1 diabetes (also referred to as juvenile or insulin-dependent diabetes) suffer from a lack of insulin because their immune systems have destroyed the pancreas’ insulin-producing islet cells.

For type 1 diabetics, gene-therapy and stem cell-based therapies hold the most promise to put an end to the daily insulin injections that many patients need to control their disease. Inder Verma, Ph.D., professor in the Laboratory of Genetics, uses gene therapy techniques to deliver insulin-making genes into non-pancreatic cells. If successful, it would allow the body to deliver its own insulin even when the pancreas’ islet cells are weakened or destroyed.

It is hoped that embryonic stem cells in laboratory dishes one day can be coaxed to develop into specific cell types, such as islet cells for therapies to replace the damaged cells of people with type 1 diabetes. The basic research of Salk scientists Fred Gage, Ph.D., Juan Carlos Belmonte, Ph.D., and Leanne Jones, Ph.D., is improving scientific understanding about stem cells.

THE LARRY L. HILLBLOM CENTER FOR DIABETES
This unique inter-institutional center, established under the directorship of Inder Verma, Ph.D., coordinates the resources and expertise of researchers at the Salk Institute and University of California, San Diego, with the express goal of advancing understanding of the molecular mechanisms causing type 2 diabetes. Together, Verma and his Salk colleagues Ronald Evans, Ph.D., Marc Montminy, M.D., along with UCSD’s Jerry Olefsky, M.D., and Shankar Subramaniam, Ph.D., with other Hillblom Center members, are pioneering ways to speed up the search for new treatment options. Analyzing and comparing patient samples with experimental data, they have already identified several dozen genes that play a role in insulin resistance. Now, they are in the process of whittling down the list, by using innovative technologies developed at the Salk Institute and hand-picking the most promising drug targets for therapeutic interventions.
Limiting DNA damage response

Chromosomes, which are the linear structures that house and protect our genes inside the nucleus of every body cell, are themselves safeguarded. Looking after the chromosomes is the cell’s DNA repair machinery. “The cell tries to fix everything to make sure that the genetic information is safe and complete for the next generation of cells,” explained Ramiro Verdun, Ph.D., a postdoctoral researcher in the lab of Salk Institute assistant professor Jan Karlseder, Ph.D., who headed the study.

So, when chromosome breaks occur, the DNA repair machinery goes into full action. But how does the repair machinery react to the ends of a chromosome during the normal process of cell division?

SAFEKEEPING HUMAN CHROMOSOMES: In this image of human chromosomes (red), the small green dots highlight the protective tips called telomeres.

When a cell divides (millions of cell divisions occur every minute in the human body), the protective caps at the ends of chromosomes come off. Without the caps, the tips of chromosomes (called telomeres) resemble DNA breaks.

If the DNA repair machinery did its normal job, these exposed broken strands would be mended by randomly fusing two chromosomes end-to-end, an abnormality that can set the stage for cancer. The Salk team found that the cell co-opts the repair machinery to deal with exposed chromosome ends, but minimizes its actions. Instead of full-blown repair, the very tips of the chromosomes are looped back, tucked in and covered with telomeric proteins, restoring the protective cap.

MOUSE BRAIN CELLS: Labeled with a green color is an adult mouse’s brain cell, which developed from a human embryonic stem cell. Mouse glial cells, a type of brain cell, are labeled blue. In red are the cell bodies of neighboring mouse neurons.

Fully functioning stem cells

Could medical treatments with stem cells one day replenish the missing or damaged brain cells that impair the lives of people with Parkinson’s or another neurodegenerative disorder? Possibly, but before recommending such therapies for their patients, doctors will want to know whether the implanted cells will safely become fully functioning members of the patient’s neuronal architecture.

And, they should, according to a recent Salk Institute study headed by Fred R. Gage, Ph.D., the Vi and John Adler Chair for Research on Age-Related Neurodegenerative Disease.

The investigation showed that human embryonic stem cells mature into fully functional adult brain cells and integrate into the existing nervous system after these human cells are injected in the developing brains of two-week-old mouse embryos.

“Besides its therapeutic potential, our finding also opens up the possibility to study human disease in a new context,” said postdoctoral researcher Alysson R. Muotri, Ph.D., a member of Gage’s research team. “We can ask if neurodegeneration is the function of an individual diseased cell or if it is caused by the local environment in the brain.”

The injected human stem cells did not restructure the mouse brains. Far less than 0.1 percent of the lab animals’ brain cells were of human origin, and those few had taken on the size and shape of their neighbors.

The experiments followed the National Academy of Sciences’ guidelines on the use of stem cells. In accordance with these guidelines and the Salk’s internal Human Stem Cell Research Guidelines, the mice were not allowed to breed.
The brains of Alzheimer’s disease patients are filled with abnormal long thread-like fibers. Salk assistant professor Roland Riek, Ph.D., and his scientific colleagues in Switzerland have solved the three dimensional structure of these fibers. The 3-D image reveals that the proteins that make up the fibrils lock onto each other much like a zipper on a jacket. This advance helps illuminate the molecular roots of Alzheimer’s and possibly other degenerative diseases of the brain.

As a result of the study, Riek and his colleagues have a better understanding about how a potential Alzheimer’s disease medication now in clinical trials in Europe interacts with the fibrils. The drug binds to the end of the fibril chain of beta amyloid proteins, halting their lethal accumulation, an early step in the formation of the amyloid plaque deposits that are a hallmark of Alzheimer’s.

Increasing the activity of two enzymes better known for their role in oxidative stress metabolism turns normally relaxed mice into “Nervous Nellies,” according to Salk Institute research.

Locally overexpressing either glyoxalase 1 or glutathione reductase 1 in mouse brains significantly increased anxiety in usually relaxed mice and made already jittery mice even more anxiety-ridden. Inhibition of glyoxalase 1 had the opposite effect.

“Currently, very little is known about the genes that predispose to psychiatric disease,” says Iiris Hovatta, Ph.D., a postdoctoral researcher in the Salk’s Laboratory of Genetics. “All of the 17 genes that we identified are very good candidates for human anxiety disorders and most of them have never been associated with anxiety-related behavior before,” added Hovatta, who along with Salk professor Inder Verma, Ph.D., worked on the study, headed by Carolee Barlow, Ph.D., while she was at Salk.

The key technology of introducing or deleting genes in the brain using viral vectors was developed in the laboratory of Verma, the American Cancer Society Professor at Salk. He said, “This is a very exciting study where we can genetically interfere with the behavior outcome, emphasizing the genetic hard wiring of certain traits.”
We often make unwise choices although we should know better. Thunderstorm clouds ominously darken the horizon. We nonetheless go out without an umbrella because we are distracted and forget. But do we? Salk Institute neurobiologists conducted experiments that prove for the first time that the brain remembers, even if we don’t and the umbrella stays behind.

Understanding how memories are stored and recalled may help discover why our memory sometimes falters.

“For the first time, we can take a look at the brain activity of a rhesus monkey and infer what the animal knows,” said Salk professor Thomas D. Albright, Ph.D., who led the research.

The Salk scientists taught rhesus monkeys to associate two random objects with each other and recorded the activity of brain cells while the monkeys tried to remember the correct pairing.

“We want the monkeys to behave perfectly on these tests, but one of them made a lot of errors,” recalled Albright. “We wondered what happened in the brain when the monkeys made the wrong choice, although they had apparently learned the right pairing of the symbols.”

Surprisingly, a subset of brain cells, which Albright believes represents the memory of the two objects belonging together, kept firing even when the monkeys chose a wrong combination.

“In this sense, the cells ‘knew’ more than the monkeys let on in their behavior,” said Albright.

Delving ever deeper into the intricate architecture of the brain, Salk Institute researchers have discovered how different types of nerve cells, called neurons, work together in tiny sub-networks to pass on just the right amount and the right kind of sensory information.

Ed Callaway, Ph.D., and his lab team revealed how specific types of inhibitory neurons in the visual cortex of a rat brain are wired to, and “talk” with, discrete excitatory neurons. They also showed how that “conversation,” aimed at keeping the right balance of chemical signals, often excludes surrounding neurons.

This new study fills in the picture of how the brain is organized into “smart” efficient networks, and researchers hope that details of this complex design might, one day, uncover the roots of such neurological diseases as schizophrenia.

“We know already that schizophrenia is a problem with organization of inhibitory circuits of neurons, and now we are uncovering how these specialized nerve cells work together and with other neurons,” explained Callaway, an associate professor at Salk.

“By understanding the brain in finer and finer resolution, we can then trace what happens when these neural circuits are mis-wired,” he adds.
New faculty at Salk Institute

The Salk Institute has welcomed two scientists, Reuben Shaw, Ph.D., and Lei Wang, also a Ph.D., as assistant professors.

- **Shaw**, who comes to Salk from Harvard Medical School, studies one of the tumor suppressor genes. Named LKB1, the gene carries the DNA recipe for a protein that is mutated in the rare malignant tumor and is frequently abnormal in people with sporadic lung adenoma, one of the world’s most widespread and lethal cancers. As described in the cover story of this newsletter, Shaw and his colleagues recently found a link between LKB1 and diabetes.

  Shaw conducted postdoctoral studies at Harvard after earning the Ph.D. degree from M.I.T., and the B.S. degree from Cornell University.

- **Wang**, who was named a Young Innovator by MIT Technology Review in 2004, is developing strategies to engineer and monitor individual molecules inside living cells by using markers that can be visualized using sophisticated methods of microscopy.

  After earning the B.S. and the M.S. degrees from Peking University in China, Wang studied at the University of California in Berkeley, which awarded him a Ph.D. degree in bioorganic chemistry. Before joining Salk, he conducted postdoctoral research in pharmacology at UCSD. Among his many honors is the Young Scientist Award from Amersham Biosciences and the journal Science.

Salk Institute’s new trustees

- **Caryl D. Philips**, a longtime supporter of graduate student training at the Salk Institute, and **Michael Pulitzer**, former chairman of a newspaper empire, recently were elected to the Institute’s Board of Trustees.

- A member of Salk’s International Council, Philips several years ago established the Jesse & Caryl Philips Foundation Graduate Student Endowment Fund to support the training of graduate students at Salk. Also a trustee of Planned Parenthood Foundation, she is manager of CDP Investments LLC. A graduate of Wright State and Wittenberg Universities, she resides and is an active community volunteer in Dayton, Ohio.

- **Pulitzer** was chairman of the board of Pulitzer Inc. Before being elected chairman, he was chief executive officer and chairman of Pulitzer Publishing Company. A graduate of Harvard College and Harvard Law School, he practiced law in Boston before working as a reporter, news editor, editor and publisher on various newspapers. A resident of Santa Barbara, he is also a member of the board of visitors of Columbia University’s Graduate School of Journalism in New York City, which awards the Pulitzer Prize that was established by his grandfather, and of the board of councilors of University of Southern California’s Annenberg School for Communication.
A Sensational Evening

“We go to many charity galas, but never, never do we expect to have fun at them, but we did at Sensational Salk!” exclaimed one of the 500 elegantly attired attendees at the Institute’s first black-tie gala, as she and her spouse reluctantly departed the Salk Institute campus late Saturday evening, Nov. 12.

“My husband and I typically leave these events after dinner and before the long speeches,” she added. “This event was different... we were sad to see the evening end.”

Festive... celebratory... simply elegant evening... with lots of time to mingle and dance to a great band was San Diego civic volunteer Marilyn Sawyer’s vision for the gala, when she and her husband, business leader Doug Sawyer, decided to chair the first Sensational Salk.

Aided by co-chairs, Carol and Jeff Chang and Dixie and Ken Unruh, the Sawyers created a gala on the Salk Institute’s campus that was fun and certainly not boring.

Sensational Salk not only introduced the Institute to business, civic, cultural and government leaders who were not yet connected to Salk, but it also served as a “homecoming” for several prominent Salk alumni and many of the friends and supporters connected to the Institute since 1965, when Salk’s centerpiece research buildings and courtyard were completed.

The centerpiece of Sensational Salk was the presentation of the inaugural Salk Medals (see related story on page 10) to Paul Farmer, M.D., Ph.D., and Donald Metcalf, M.D.

Sensational Salk also recognized the 50th anniversary of the polio vaccine that was developed by Jonas Salk, M.D., one of the true heroes of the 20th century. Believing that the best reward for doing good is the opportunity to do more for humanity, Salk went on to establish, in 1960, what is today the Salk Institute for Biological Studies. Both Salk and Kahn have died. However, their sons attended the gala. Also present were officials of the event’s “signature sponsor,” HellerEhrman LLP, and “superior INSIDE SALK

They could have danced (almost) all night at Sensational Salk.

(Left to right) Jeff and Carol Chang, co-chairs, and Marilyn and Doug Sawyer, chairs of Sensational Salk.
One of the many signs of success at a black-tie gala is the attendees’ reluctance to go home. At 10:30 p.m., the band stopped performing because its contract required that it do so. The couples happily crowding the dance floor sighed and begged the band to continue.

“Sensational Salk was a very successful ‘friend-raiser,’” said Ms. Sawyer. “It was a perfect way to celebrate the Salk Institute and its research to benefit humanity.”

Sawyer became acutely aware of the importance of research to benefit humanity one year ago, when her beloved sister was diagnosed with chronic myelogenous leukemia (CML).

“While reading everything that we could find about CML on the internet, Doug and I kept seeing references about how Dr. Tony Hunter’s research at Salk contributed to the development of Gleevec, a drug that is saving my sister’s life,” she explained.

Since FDA approval in 2001, Gleevec has added years to the lives of thousands of people with CML. Hunter’s and Bart Sefton, Ph.D.’s research at Salk, conducted over 20 years ago, helped lay the groundwork.

Marilyn’s sister attended Sensational Salk, and at dinner she sat next to Hunter. She too was reluctant to end the evening.
The first Sensational Salk honored two exceptional individuals whose life work has taken very different approaches to helping humanity. The individuals — Paul Farmer, M.D., Ph.D., and Donald Metcalf, M.D. — were awarded the inaugural Salk Institute Medals.

The two medals represent "the dual passions of Jonas Salk: public health and basic research in the biological sciences," said Richard Murphy, Ph.D., the Institute’s president and CEO.

Farmer, who is dedicated to improving the health care of the people of Haiti, Rwanda and other impoverished areas of the world, received the Salk Institute Medal for Health and Humanity.

Receiving the second honor, the Salk Institute Medal of Research Excellence, was Donald Metcalf, M.D., whose research on cancer has improved the treatment of this disease.

Designed by the artist Paloma Picasso, the medals recognize the 50th anniversary of Salk’s development of the first safe and effective polio vaccine, and the 40th anniversary of the opening of the Salk Institute’s research campus, designed by the famous architect Louis Kahn in collaboration with the vaccine pioneer.

Farmer, who divides his time between Boston and the rural areas of Haiti and Rwanda, was the subject of the popular book, Mountains Beyond Mountains: The Quest of Dr. Paul Farmer, a Man Who Would Cure the World, authored by Tracy Kidder. In Boston, he is an attending physician and Professor of Medical Anthropology at the Brigham and Women’s Hospital.

"Paul Farmer is exceptional in his thinking and his life work," said Jerome Kohlberg, chair of Salk Institute’s Board of Trustees. “He has shown the world that poverty can be addressed.”

The basic research discoveries of Metcalf, who is Professor Emeritus at the Walter and Eliza Hall Institute of Medical Research Melbourne, Australia, enabled the development of biological agents to accelerate the regrowth of blood cells in people with cancer, following chemotherapy, bone marrow or peripheral blood transplantation. Medications based on his research are now in extensive clinical use throughout the world.

Metcalf showed "courage, tenacity, and vision in carrying his laboratory discoveries to the clinic," said Salk professor Joanne Chory, Ph.D., chair of the faculty committee that reviewed nominations for this Salk Medal. “This is indeed remarkable, a dream few scientists have achieved.”
2005 was an outstanding year for the Salk Institute. Our scientists continued to create new knowledge to benefit humanity, we honored Jonas Salk by celebrating the 50th anniversary of his polio vaccine and the 40th anniversary of the Salk Institute, and we memorialized our most important partnership by dedicating one of the Institute’s masterpiece buildings to the March of Dimes. Looking back, 2005 is a tough act to follow, but looking forward, 2006 stands to be even better, for it will be a year of planning to guarantee Salk’s future as one of the world’s truly exceptional research institutes.

To further strengthen the Institute’s science and administration, the Salk community will carry out a strategic planning exercise, our first since 2001. This self-assessment process will evaluate our research programs and administrative operations and will benefit from the objective opinions of outside experts.

We will continue to plan for the public opening of the Institute’s first Capital Campaign, to bring resources to the Institute and create a fundraising capacity that will serve our needs for years to come. Thus far, during the campaign’s silent phase, funds garnered from the March of Dimes, foundations, trustees, and other generous benefactors have had an enormous impact on the Institute’s operations. They have allowed us to recruit 15 new scientists to the faculty, to purchase sophisticated scientific equipment to expand the investigative reach of our scientists, and to establish or strengthen research units to explore human embryonic stem cells, cancer, chemical approaches to biology, computational neuroscience, and bioinformatics. We have also increased our endowment, which, with pledges, now approaches $150 million. Growing the endowment will be essential for ensuring the Institute’s long-term future.

The Campaign’s priorities will spring from the upcoming strategic plan and will doubtless include continuing to build the endowment while providing research support for our existing faculty in the lean times we now face. The National Institutes of Health and the National Science Foundation, traditional sources of federal support, are under severe pressure from our cash-strapped government, and internal sources of support from the private sector will be essential if the Salk Institute and organizations like it are to fulfill their missions.

In 2006, the Institute will seek city government’s approval of our campus development master plan, which will allow the Institute, over the coming decades, to build facilities to accommodate its expanding research, administrative and employee needs. The plan was carefully drawn to allow expansion without compromising the Institute’s fragile seaside environment or its renowned architectural character, and it remains true to the original vision of Louis Kahn and Jonas Salk.

Salk is home to some of California’s most well-known stem cell experts, and other Salk faculty, while not yet working in the stem cell field, conduct research programs fundamental to understanding how stem cells differentiate. At the moment, Proposition 71’s funding for California stem cell research is at a standstill because opponents of the research have prevented the issuance of research-supporting bonds by arguing in the courts that Proposition 71 was unconstitutional. However, we expect to prevail, and if so, state funds will begin flowing during this or next year.

Finally, the most exciting developments of 2006 will come not through planning, but from our faculty’s research. No one can predict where science will track in the new year, or where results will lead us — and history shows that great advances often result from serendipity. Nonetheless, responsible long-range planning to strengthen the Institute’s scientific, administrative and financial futures will enhance the environment in which the creative thinking and research of our faculty takes place, and their contributions to humanity will surely flourish.

Richard Murphy, President and CEO

Richard Murphy, President and CEO
In 1960, just five years after developing the first safe, effective vaccine against polio, Jonas Salk, M.D., founded the institute that today bears his name. Home to 11 Nobel laureates since its founding, the Salk Institute for Biological Studies is a world leader in basic research on the biological principles governing life at all levels, from the individual cell to an entire population. For more information: www.salk.edu.

Calendar

**AUGUST 26**

**Symphony at Salk**

Please note: the above represents a selected event. For additional information about this and other Salk events, please contact Institute Relations at 858.453.4100 ext. 1200.

**Sign-up for Update**

Richard Murphy, Ph.D., Salk Institute’s president and CEO, has launched a free electronic newsletter, called *Update for Salk Institute Friends*, that briefly describes recent research discoveries and upcoming public events. To sign up, email: update@salk.edu.

**New video about Salk Institute**

Premiered at *Sensational Salk* (please see pages 8-10 of this issue) was a new video, now posted at: www.salk.edu

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**HONORING MARCH OF DIMES:**

This plaque, recently mounted on an exterior wall of the Salk Institute’s north research building, recognizes the March of Dimes (MOD)’s over 40-year relationship with the Institute. MOD provided the seed money that enabled Jonas Salk, M.D., to fulfill his vision for a research institute dedicated to revealing the basic principles of biology.