THE DANA FOUNDATION'S

BRAINWORK

The Neuroscience Newsletter

Vol. 15 No. 2 March-April 2005

News FROM THE FRONTIER

••• Sad simians in neuroscience. A group of female cynomolgus monkeys in Winston-Salem, N.C., are poised to offer valuable new information about depression in humans—particularly in women, who account for nearly 12 million of the 19 million cases diagnosed each year in the United States. The study of these monkeys, led by Carol Shively, professor of pathology at the Wake Forest University School of Medicine, introduces the first primate model of adult depression.

Animal studies of depression have labored under several drawbacks. The standard model has been the rodent, whose brain lacks the complex neural circuitry that underlies mood and emotion in the human brain; moreover, the study populations have been almost exclusively male. In addition, although rodents live in groups in the wild, in the laboratory they have usually been housed in social isolation, one to a cage. Finally, the stimuli commonly used to produce stress (such as a movement-constraining harness or the administration of small electric shocks

(Continued on page 7)

Inside:

Recalling Freud

Researchers Uncover Voluntary Repression of Memories

BY HAKON HEIMER

The truth is that we all live by leaving behind …

—Jorge Luis Borges,
Funes the Memorious

The title character of Jorge Luis Borges's short story *Funes the Memorious* lives a tortured life: a riding accident left him without the ability to forget. He spends his days alone in the dark, trying to avoid adding to the store of memories that constantly impinge on his consciousness.

It would be impossible to function if we were not able to block out all but the relevant memories. Indeed, the ability to not dwell on distracting or unpleasant experiences is a vital coping mechanism. Thus, the brain must have ways to suppress memories.

Sigmund Freud studied not only ways in which the brain might unconsciously block unwanted memories, but also the idea that we might actively, consciously help ourselves forget.

Influenced strongly by the ideas of Sigmund Freud, Western society has long entertained the idea that the mind has mechanisms to suppress especially traumatic unwanted memories. We take it for granted that Freud was focused only on ways in which the mind might unconsciously, and automatically, block access to unwanted memories, but Freud also proposed that such forgetting may be served by a more active, conscious process. The mechanisms that might underlie such an ability have remained unclear and difficult to investigate, but recently psychologists and neuroscientists have taken fresh aim at this subject.

Don't Think!

In a study in 2001, researcher Michael Anderson of the University of Oregon demonstrated that the brain could be made to suppress unwanted memories. His method, termed "think/no think," was quite simple: he asked subjects to study a pair of words. The next time they saw one of those words, he asked them to *not* think about the word with which it had been paired. With repetition, subjects indeed had a harder time recall-

(Continued on page 2)

(MEMORY, continued from page 1)

ing the response (or target) word than subjects who had not been instructed to suppress the word.

So is the memory for the suppressed words still there? Based on related research, Anderson is inclined to think so, though there is no direct evidence of whether the memory itself has been diminished, or simply the ability to access it.

Anderson wonders whether his think/no think paradigm replicates what might be at work with more complex memories, especially traumatic memories. "When we see something in the environment that's upsetting, we put up a mental hand that signifies, 'I don't want to think about that right now,' without necessarily having the intention to forget anything," says Anderson.

Once More, with Emotion

Anderson's findings have been thrust into some highly charged debates, including those about the recovery of "lost" memories in cases of childhood abuse. But they may also be relevant to some psychiatric disorders in which people suffer from the intrusion of unwanted thoughts: posttraumatic stress disorder, obsessive compulsive disorder, and some forms of anxiety disorders and depression.

Anderson acknowledges the critics who question whether something as simple—and emotionally neutral—as memory for words proves that more complex, emotionally charged personal experiences could be actively forgotten. Marie Banich and her colleagues Brendan Depue and Tim Curran at the University of Colorado have taken an initial step in expanding Anderson's findings. In a recently completed study that has been submitted for publication, they have adapted Anderson's think/no think method to investigate whether the same effects would hold for words with emotional content, as well as more complex information such as very unpleasant visual scenes.

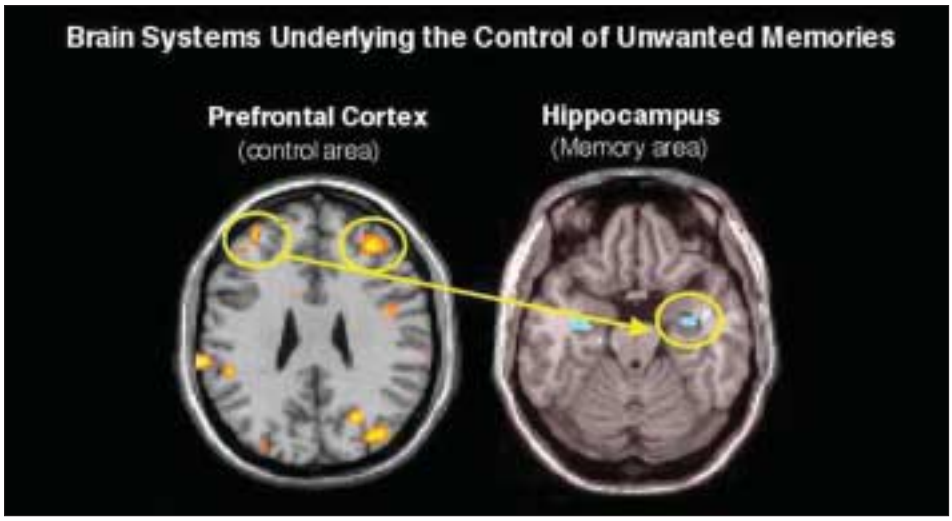
In a first round of experiments, Banich and colleagues used photographs of faces as cues and paired these with word targets that were either emotionally neutral (such as "carriage") or likely to evoke an emotional response (such as "murder"). The researchers found that even with the image cues and emotion-laden word targets, study subjects were able to suppress the memories when instructed not to think about them.

Still, because research has shown that emotional content helps solidify memories, Banich and colleagues expected to find it more difficult to suppress emotional words. Surprisingly, they found the opposite: subjects did a better job of suppressing the memories of emotion-laden words than of neutral words.

"Our interpretation of these effects is that the more salient an item is, the better your ability to exhibit cognitive control over it," says Banich. A similar result was found in subsequent experiments when the word targets were replaced by image targets, either neutral scenes such as a wildlife photo or emotional ones such as a photo of a burn victim.

At the University of Washington, Susan Joslyn and Mark Oakes have focused on real-life memories of their subjects to assess whether truly complex memories are subject to the same voluntary forgetting as word lists. In a soon-to-be-published series of experiments, Joslyn and Oakes asked subjects to write short accounts of daily episodes in their lives. Then, on an invented pretext, some of the subjects were asked to forget those memories, and continue writing up accounts of new episodes (a method called "directed forgetting").

The researchers even set up one of



Researchers found that while study subjects tried to suppress memories, the prefrontal cortex became more active and the hippocampus became less active. This finding indicates inhibition of memory processes.

The Neuroscience Newsletter

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their experiments to run during the week of Valentine's Day, the idea being to ensure that many of the memories thus recorded would have emotional value. Later, when tested on their recall of those events, subjects who had been directed to forget about the Valentine's week events were less able to remember those events than subjects who had received no such instructions.

The next things to uncover, Joslyn says, are the psychological mechanisms and strategies that people employ to forget things. "With directed forgetting of word lists, it has been suggested that people remember items they are directed to forget less well because they rehearse them less often. Another possibility is that people suppress or inhibit the memory so that it's less available at recall," she says. For the think/no think form of forgetting that Anderson and Banich's group studies, the latter—suppression of the memory—appears to be the case.

Another direction for this research is to understand how the brain controls which memories are available for access.

Forgetting in the Brain

Another direction for this research is to understand how the brain controls which memories are available for access. Last year Anderson, in collaboration with John Gabrieli and others at Stanford University, reported on a study using magnetic resonance imaging to track brain activity as study subjects obey the "don't think" command. They found that two important brain areas—the prefrontal cortex and the hippocampus, a structure critical for memory formation—changed their activity levels while subjects were trying to suppress memories. The prefrontal cortex became more active, while the hippocampus became less active, suggesting an inhibitory effect on memory processes. Indeed, Anderson and colleagues were able to predict how much memory suppression a subject would show on a later test by how much activity they measured in the prefrontal cortex while the subject obeyed the "no think" instruction.

The involvement of the prefrontal cortex was particularly interesting to Anderson because it suggests that the suppression of memory is effected in the same way, by the same brain centers, as the suppression of movements. He likes to use an example from personal experience to illustrate: he once reached to grab a plant falling from a window sill, but halted his reflexive action when he realized it was a cactus. Such overriding of reflexes (called "executive control") is exercised by regions of the prefrontal cortex, which can directly influence the brain centers that control reflexive behaviors. Anderson proposes that in his think/no think paradigm, executive control is also being exerted by the prefrontal cortex on the hippocampus to suppress memory in much the same way.

Borges's character Funes the Memorious was buffeted by memories to the point that it made it hard to sleep. At night Funes tried to sleep by focusing on some newly built houses that he had never seen. "Funes imagined them black, compact, made of a single obscurity; he would turn his face in this direction in order to sleep," writes Borges. Perhaps the research being conducted into the suppression of memory will offer more permanent solutions to patients with disorders that force unwanted memories into their consciousness.

Hakon Heimer is a science and medical writer in Providence, R.I.

In Search of Therapy:
The Genetics of Deafness

BY RABIYA S. TUMA

Hearing loss is the most common form of sensory impairment in humans; one in 1,000 children is born profoundly deaf and 10 percent of people over the age of 65 experience communication problems because of progressive hearing loss.

Although scientists have had a detailed understanding of the mechanics of the system for several decades (see sidebar) and knew that both genetic mutations and environmental trauma can cause deafness, it has been since only the mid 1990s that they have begun to learn how the ear works at the molecular level and what genetic mutations lead to deafness.

"Without information about the molecules it is impossible to develop real therapeutics," says Christine Petit, a professor at the Pasteur Institute in Paris and a leader in the genetics of human deafness. To understand hearing impairment at the level of proteins, Petit and other researchers have worked to identify genetic mutations that cause deafness in humans. Already 42 genes have been identified, and another 40 or so are in the works.

Mutations in the human gene *GJB2*, which encodes the protein connexin26, are the most common cause of inherited deafness, and *GJB2* was the first gene to be associated with hearing loss. Researchers have learned that the connexin26 protein works not in the sensory cells, but rather in the supporting cells nearby.

When the sensory hair cell detects a sound wave, the opening of its ion channels causes it to release neurotransmitters—glutamate and potassium—at the synaptic junction that connects it to the auditory nerve. Some of the neurotransmitter released is taken up by the auditory nerve itself, and is used to carry the signal to the brain. But scientists think it is the job of the

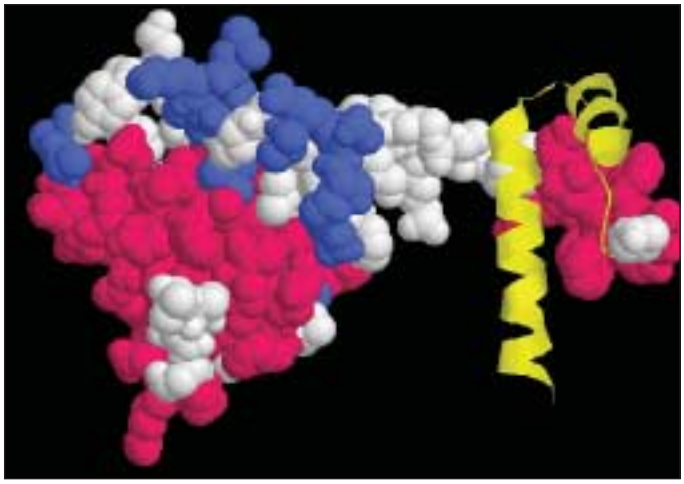
(Continued on page 4)

(DEAFNESS, continued from page 3)

supporting cells to quickly scavenge excess neurotransmitter molecules from the area so that the system is free to work when the next sound happens.

Petit and others suggest that mutations in connexin26 disable the supporting cells, prohibiting them from rapidly vacuuming up the glutamate and potassium and leaving the system insensitive to subsequent sounds.

Researchers have found that unlike *GJB2*, most of the genes that cause deafness do so in a small percentage of deaf people. Finding these genes is tricky. To do so, researchers often rely on large families in which several individuals are affected.



A three-dimensional model shows a portion of the POU4F3 *gene. The yellow ribbon represents a portion of protein truncated because of a mutation in the gene, leading to hearing loss.*

Karen Avraham of Tel Aviv University and colleagues identified a mutation in the *POU4F3* gene that is responsible for deafness in a large Jewish family. The scientists interviewed the family and took blood samples from family members interested in participating. They then drew a pedigree of the family and compared DNA isolated from family members who had significant hearing loss with that of hearing family members.

"The search for the gene … began when a member of the family, named Family H, contacted our laboratory at the Sackler School of Medicine," Avraham says. The first ancestor the family knew to have suffered from hearing loss was a man born about 1843 in Libya. One of his four children inherited the progressive hearing loss. That individual had seven children, four of whom also suffered hearing problems, as did six out of seven children in the subsequent generation. "Most of our studies were done with this generation," Avraham says.

The team narrowed down the location of the mutation that caused Family H's hearing loss to a relatively small region of Chromosome 5, but they could not identify the specific gene from the family data, so they turned to mouse genetics for more detailed analyses. They identified the corresponding chromosomal region in the mouse genome, then tested the genes within that region to see if any encoded proteins that were expressed in the inner ear.

The researchers found that one of these genes, *Pou4f3*, was expressed in hair cells. Furthermore, mutations in the gene caused deafness in the mice.

With that information in hand, the researchers knew where to look in the DNA from affected Family H members. Sure enough, they found that these individuals, but not the hearing members of their family, were missing eight nucleotides in the *POU4F3* gene. That mutation resulted in a nonfunctional protein.

The protein encoded by *POU4F3* binds to DNA and regulates the activity of other genes. Avraham's group has now started to identify some of these target genes, which themselves are critical for hair cell function. One of them is *GFI1*. When *GFI1* is absent, the hair cells do not survive, which would lead to the type of progressive hearing loss seen in Family H.

Although researchers such as Avraham and Petit do not yet have ways to correct the mutations they have identified, this sort of information already has value to people who have deafness in their families, says Richard J. Smith, director of the Molecular Otolaryngology Laboratory at the University of Iowa. Many of the families and patients he sees in his clinic want to have genetic testing done.

"If they have a child born deaf, they often have a lot of guilt wondering if they did something wrong—a concern that is not particular to deafness," Smith says. "If it is a genetic mutation, at least you have an answer to what caused the problem.

Also, for some mutations, especially common ones such as *GJB2*, clinicians can use genetic information to help direct treatment and tell parents whether further deterioration in hearing is likely.

(Continued on page 8)

THE ANATOMY OF HEARING

Using physiological and anatomical studies, scientists have learned that sound waves are converted into electrical impulses by sensory cells in the inner ear. As the sound waves hit the ear drum, the mechanical pulses pass to three small bones in the ear, then on to the cochlea, a fluid-filled space in the inner ear.

It is here that the sensory cells reside. These cells, called hair cells, have small protrusions on their surfaces called cilia, which look like short hairs. As the sound waves pass through the inner ear fluid, the fluid bumps against the hairs, like wind blowing the tops of trees. When the sound is loud enough, the waves move the cilia, causing filaments inside the cilia to pull open ion channels and initiating a neuronal electrical signal. This signal is then passed from the sensory cell to the auditory nerve fibers and on to the brain, where the signals are processed.

New Clues Emerge in Hunt for Autism Gene

BY ELIZABETH NORTON LASLEY

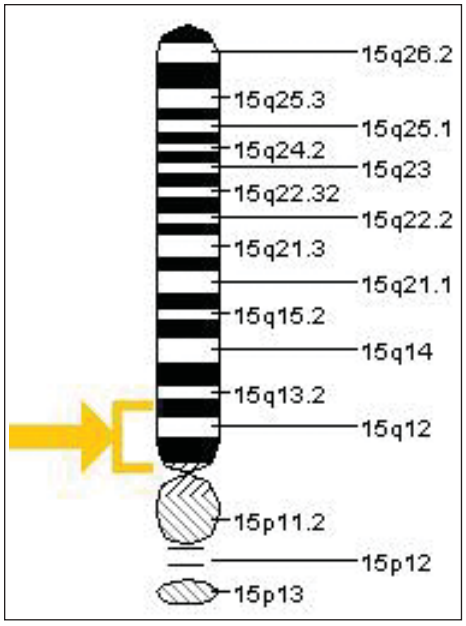
Autism, a spectrum of often heartbreaking behavioral traits, also can be studied as a mystifying collection of genetic variants. Several lines of research are converging to show how opposing genetic pathways can lead to autism—perhaps laying important groundwork in understanding the biology of the disorder.

"We'd all like to move in a straight line from the gene to the brain changes to the behavior," says Ed Cook, an autism researcher at the University of Chicago. "But there are many steps in between." Intriguing new clues are showing what some of these steps might be.

One of the more frequent genetic anomalies is found on chromosome 15. Normally a person inherits one set of chromosomes from each parent, but in 1 to 3 percent of patients with autism, extra copies of a particular stretch of DNA are inherited from the mother but only one from the father. The double or triple dose of this region, designated 15q11-q13, is noteworthy because the same portion of maternal DNA is absent in most cases of a related condition, Angelman syndrome. Patients with this latter syndrome show mental retardation and signs that can be diagnosed as autism, including absence of speech, epilepsy, and movement difficulties.

Despite seemingly opposite effects on this chromosomal region, both circumstances can lead to autism. One explanation may lie in a gene called *UBE3A,* a so-called imprinted gene, meaning that the paternal or maternal copy is expressed in varying proportions. Normally *UBE3A* is expressed in a maternal-specific manner, particularly in the brain; the paternal copy is "silenced" or inactivated. The absence of this gene from the maternal chromosome is a cause of Angelman syndrome.

This maternal-specific phenomenon, along with another gene that may be involved, holds clues to autism and related disorders. The second gene, termed *MECP2,* mutates in a third neurological condition, Rett syndrome, which overlaps with autism in several ways: delays in development, language impairment, and repetitive movements. *MECP2* is located not on chromosome 15 but on the X chromosome. Thought to play a role in silencing other genes, *MECP2* is



The UBE3A gene is located on chromosome 15. Extra copies of DNA from this region have been associated with autism; an absence of maternal DNA from the same region correlates with Angelman syndrome, a related condition.

believed to act at an important control region near *UBE3A* to help regulate the gene.

To test whether boosting levels of *MECP2* would be a therapeutic option for Rett syndrome, Huda Zoghbi and colleagues at Baylor College of Medicine, Houston, developed a line of transgenic mice that express higher than normal amounts of the gene's protein product, MeCP2. Their findings, published online Sept. 6 in *Human Molecular Genetics,* have implications for autism as well. After a period of normal development—consistent with both Rett syndrome and some cases of autism—the transgenic mice began to show signs of neurological disorder, including seizures and paw-clasping; many stopped grooming themselves and died prematurely.

The authors do not draw overt parallels between mice overexpressing *MECP2* and human patients with autism. However, Janine LaSalle and colleagues at the University of California, Davis, medical school have found increased levels of *MECP2* in a few patients with autism or autism-like disorders—suggesting that excessive amounts of *MECP2* may be a factor in autism.

"Our findings unequivocally show that doubling *MECP2* levels affects brain development and plasticity, making duplications of this gene a potential mechanism in some cases of autistic disorders," says Zoghbi.

UBE3A complicates the picture. LaSalle and colleagues have shown that mice lacking *MECP2* have low levels of *UBE3A*. Because absence of *UBE3A* is a hallmark of Angelman syndrome, the research again seems to conflict: too much or too little *MECP2* results in two distinct disorders, both of which share features with autism. The team's report, published online Dec. 22 in *Human Molecular Genetics*, shows how apparently contradictory biochemical pathways may converge to produce the syndrome of autism.

Studying brain tissue taken after death from patients with Rett syndrome, Angelman syndrome, and autism, the authors found reduced levels of both *UBE3A* and *MECP2*, mirroring the findings with the transgenic mice. They also found reductions in another gene that may be one missing piece of the puzzle.

Located in the suspect region of 15q11-q13, this gene, *GABRB3*, encodes for part of a receptor for gamma-aminobutyric acid (GABA), a neurotransmitter that slows brain cell activity. According to James Sutcliffe, a genetics researcher at Vanderbilt University, "It's possible that overexpression not only of *UBE3A* but of *GABRB3* contributes to autism in

(Continued on page 6)

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people with extra copies of 15q11-q13." On the other hand, Sutcliffe surmises, abnormal imprinting control in this region (presumably involving *MECP2*) may explain the reduced expression of these genes in Rett syndrome and some cases of autism.

"It's an exciting finding," Sutcliffe says, noting that linkage studies—which look for culprit genes in families with autism—point to the region of 15q11-q13 containing *GABRB3* and

As the roles of these and many other genes become better understood, scientists will develop a clearer picture of what happens in the brain to produce autism and related disorders.

two other genes that function in GABA receptors. As the roles of these and many other genes become better understood, scientists will develop a clearer picture of what happens in the brain to produce autism and related disorders.

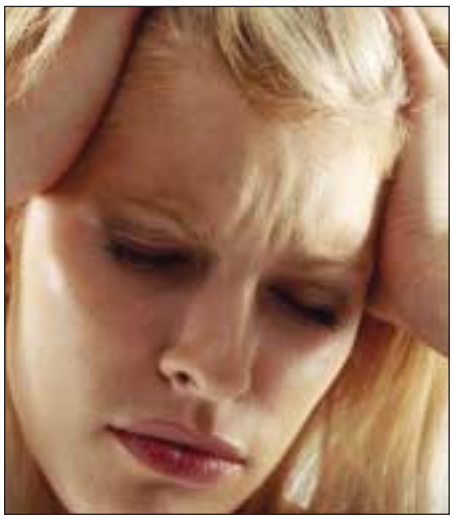
Zoghbi hypothesizes that mutations in these genes disrupt plasticity (the process through which brain cells make connections), strengthening or weakening the connections depending on specific experiences. Incremental gains can and do lead to new treatments: clinical trials are under way to see whether a drug to enhance synaptic strength can improve memory, language, and behavior in adults with Fragile X syndrome, an inherited form of mental retardation. Although autism research has not yet reached this level, work on the foundation has begun.

Elizabeth Norton Lasley is a freelance science writer in Woodbury, Conn.

A Critical Link between Chronic Stress and Aging

BY BRENDA PATOINE

You may know that chronic stress is bad for your health, but a widely publicized study now tells us it could take a decade or more off your life. The study found that chronic psychological stress effectively shaved the equivalent of 9 to 17 years off the length of telomeres, the structures at the tips of chromosomes that serve as a yardstick of biological age. The report, published in *Proceedings of the National Academy of Sciences* in November, is the first to show a direct



In women with higher stress levels, chromosomal structures called telomeres have been found to be shorter. Telomeres are a measure of biological age. The finding may indicate a biological mechanism by which stress can shorten the lifespan.

link between chronic stress and aging, and it hints of a possible biological mechanism for how stress can shorten lifespan.

The researchers, led by University of California, San Francisco clinical psychologist Elissa S. Epel and molecular biologist Elisabeth H. Blackburn, studied 39 mothers who were caring for a chronically ill child and compared them with 19 mothers of healthy children. They measured the length of telomeres in samples of the women's white blood cells, which play critical roles in immune function, and assessed the levels of telomerase, an enzyme that can extend shortened telomeres. They also looked at cellular indicators of oxidative damage, a sort of "biological rusting" caused by free radicals that has been linked to aging and age-related diseases.

The researchers found that women who were more stressed, as measured both objectively (years spent caregiving) and subjectively (self-perceived stress levels), had shorter telomeres, lower levels of telomerase, and higher oxidative load. "We saw a clear association between the number of years of caregiving and the excessive telomere shortening and excessive loss of telomerase activity," says Blackburn. "It looks pretty much like cause and effect—that it's the stressful situation that is driving those read-outs in the cell."

"This is a provocative finding in the best sense of the word," said Stanford University stress expert Robert Sapolsky in a commentary published in *Proceedings of the National Academy of Sciences.* If the finding can be replicated and generalized to other populations, he wrote, it may ultimately "reveal a detailed pathway by which stress can influence a fundamental aspect of the aging process."

Telomeres and telomerase have become the focus of intense study in aging research, a sort of fountain of youth at the most fundamental biological level. Each time a cell divides, its telomeres shorten a bit. At a certain threshold, the cell can no longer divide and begins to deteriorate. As cell populations throughout the body deteriorate, the physical effects of aging become apparent: hair turns gray, skin wrinkles, joints and bones weaken, organ systems begin to fail, and cognitive deficits appear.

Numerous scientific reports have documented the progressive shortening of telomeres with age, and at least one study has shown that shorter telomeres are associated with all causes of death in the elderly.

Blackburn cautions that the initial finding, from a small though well-controlled group of subjects, does not prove a mechanistic pathway from stress to increased oxidative damage to lower telomerase to shortened telomeres. "All we have are observations, clinically and in the lab—sets of numbers that all point to danger signals based on everything we know from previous studies of cells in the lab," she says. "But we can't say who's pushing what."

Researchers are now working to nail down the precise mechanisms by which stress leads to premature aging.

Nonetheless, the study has created a stir in the aging-research community. Caleb E. Finch, an expert on genomic regulation of aging at the University of Southern California, calls it "a pioneering investigation" that "opens the door to a new set of processes in human health."

Blackburn, Epel, and their colleagues are now working to nail down the precise mechanisms by which stress leads to premature aging, and to try to generalize the findings to other populations and cell types. They have initiated studies to look at telomere length and telomerase activity in people with depression and in people who are undergoing stress-intervention programs. They want to know, for example, how yoga, meditation, or other proven stress-management techniques might impact these cellular measures of aging.

"We don't know yet if this finding generalizes at all," Blackburn said. "We have no reason to think it doesn't, but until you ask the question, you can only guess."

Brenda Patoine is a freelance science and medical writer based in LaGrangeville, N.Y. She can be reached at bpatoine@aol.com.

News
FROM THE FRONTIER

(Continued from page 1)

to the foot) do not correspond well with sources of stress in the animals' natural setting.

As they explain in the April *Journal of Biological Psychology,* Shively and colleagues have broken with tradition by developing a primate rather than a rodent model for depression, by using only females in their study population, and by focusing on "social stress"—that is, the day-to-day demands, rebuffs, and shifting alliances of a typical community.

The researchers have established that the chronic stresses of life in a social group can indeed bring on depression in susceptible individuals. At the same time, they have developed an animal model that may permit more accurate testing of possible new treatments for depression. Next, Shively says, "We will be looking inside the monkeys' brains with PET imaging, perhaps even getting pictures of some antidepressant treatments at work."

••• **Prions require high-tech hunting.** When mad cow disease and its human equivalent, Creutzfeldt-Jakob disease (CJD), were traced in 1997 to an infectious particle called a prion, the discovery brought neurologist and biochemist Stanley Prusiner a Nobel Prize. The next step seemed clear: find a way to detect disease-bearing prions in brain tissue.

Zeroing in on abnormal prions in living brain tissue has proved very difficult, however. The two techniques most commonly used—immunohistochemistry and microscopic examination of the tissue—are moderately sensitive, but they cannot detect abnormal prions at low levels. Indeed, up to now a definitive diagnosis of prion disease in an animal or human patient has been available only after autopsy.

An article in the March 1 *Proceedings of the National Academy of Sciences* describes an advance in this field that may allow the diagnosis of prion disease in brain biopsies from living patients. Neurologist Jiri Safar of the UCSF Institute for Neurodegenerative Diseases (which Prusiner directs), and his collaborators call their technique the CDI, or conformation-dependent immunoassay. The great sensitivity of the CDI comes from the application of a new type of antibody that can recognize abnormal prions in a tissue sample by their distinct molecular shape.

••• **Migraine, aura, and the risk of stroke: What's the connection?** People who suffer from migraine headaches tend to show a higher incidence of ischemic stroke (blockage of a blood vessel) than the general population. The correlation is particularly strong in young women who experience an "aura"—a disturbance of vision or other senses—just before or during the migraine. However, say researchers Lenore Launer and her co-authors in the February 22 issue of *Neurology,* "Why migraine with aura might increase the risk of early-onset ischemic stroke is presently unknown."

The research team led by Launer, an epidemiologist at the U.S. National Institute on Aging, worked with researchers from the Netherlands National Institute of Public Health and the Environment to compare the medical profiles of 620 people with migraine to those of 5,135 migraine-free control subjects. The migraineurs scored higher than the control group on several cardiovascular risk factors. Smoking and a parental history of early heart attack were more common among people with migraine; in addition, high blood pressure and poor cholesterol levels were more common in those who had migraine with aura. The finding that migraineurs were more likely to have parents with early heart disease raises the possibility of a shared predisposition that makes some people more susceptible both to cardiovascular disease (including stroke) and to migraine headaches.

••• **Early detection of Alzheimer's disease.** One of the first examples of nanotechnology being put to use in the

(Continued on page 8)

(DEAFNESS, continued from page 4)

These human genetic studies may lead to molecular therapies. For example, scientists recently showed in mouse experiments that when they blocked the expression of another gene, *Rb*, support cells in the cochlea transformed into sensory hair cells. If investigators find ways to replicate the result in humans, they might be able to help people who have degenerative hearing loss because of damage to hair cells.

"That is the real challenge," Petit says. "If we can move from hypothesis to treatment, and restore the function of the cochlea, that would be fantastic."

Rabiya S. Tuma is a science and medical writer in New York, N.Y.

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(NEWS, continued from page 7)

service of medicine is a new, extremely sensitive technique for finding minute amounts of certain disease proteins in bodily fluids. Bio-barcode amplification, or BCA, is the work of a research team led by Chad Mirkin of Northwestern University. In the February 15 *Proceedings of the National Academy of Sciences,* Mirkin and a Northwestern colleague, neuroscientist William Klein, describe how the BCA technique employs nanoparticles, each one smaller than a single human cell, to search for markers of disease in human cerebrospinal fluid.

In Alzheimer's disease, the marker is known as ADDL, for amyloid-beta-derived diffusible ligand. This is a subunit of the protein that aggregates into the nerve-entangling amyloid plaques that come to riddle the brain in the late stages of the disease.

For decades, the presence of these plaques and neurofibrillary tangles in the brain has been the only definitive evidence of Alzheimer's disease, and this evidence is available only in a postmortem examination. But because the BCA technique can detect the presence of small ADDL molecules even at the lowest levels, it raises the exciting possibility of an accurate diagnosis years earlier, even before the onset of disease. Early diagnosis would, in turn, allow much more time for treatments aimed at attenuating or at least delaying later symptoms.

"This is an exciting development, not only for neurodegenerative diseases like Alzheimer's disease but also for many forms of cancer and for infectious diseases such as HIV-AIDS, in which the ability to study and validate new markers for these ailments requires extraordinarily sensitivity," Mirkin says.

Sandra J. Ackerman is a science writer based in Durham, N.C.

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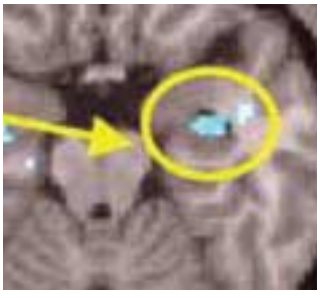

Memory Repression