THE DANA FOUNDATION'S

BRAINWORK

The Neuroscience Newsletter

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News FROM THE FRONTIER

••• **Hostile teens may be prone to heart disease.** Among adults, "type-A" behavior and heart attacks go together like business suits and three-martini lunches, but new research suggests that as early as childhood or adolescence, a hostile personality may set the stage for cardiovascular disease. In an initial screening and again after an average of three years, researchers at the University of Pittsburgh and the University of Helsinki evaluated groups of children ages 8 to 10 and 15 to 17 for signs of hostility, with a standard scale that used the subjects' own self-assessments as well as reports by trained observers. The team also measured blood pressure, body mass index, insulin resistance, and levels of blood triglycerides. If two or more of these factors were in the top 25 percent for the subject's age, race, and gender group, the child was considered to have "metabolic syndrome," a cluster of conditions known to lead to cardiovascular disease.

The researchers found that in both children and adolescents, those with high hostility scores at the first screening were more likely to show the

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REGENERATIVE MEDICINE:
Stem cell therapy is causing a stir, but many questions remain. Page 4

GETTING SLEEPY? Page 6

I Feel Your Pain (and Joy):

New Theories About Empathy

BY ANN MACDONALD

A man winces while recalling a painful medical test, and a friend listening to the account grimaces in response. A woman beams as she tells a business colleague about receiving a promotion and the colleague smiles back. Empathy—the ability to share another person's emotions, thoughts or feelings—is generally believed to be one of three capacities that distinguish people from other animals (along with language and the ability to make tools). Yet even as neuroscientists have identified brain processes involved in language and learning, the neural roots of empathy remained elusive.

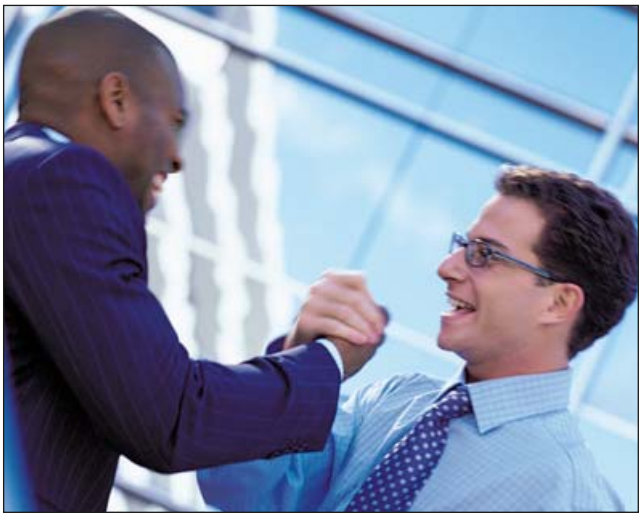
That may be changing, thanks to several lines of research that have recently converged. In the process, new findings about empathy are providing support for controversial ideas first raised centuries ago. Among those receiving renewed interest is the philosopher Benedict (Baruch) Spinoza, who in the late 1600s proposed that body, mind, and emotions are linked—and was denounced for it.

Although today's researchers differ on some details of how empathy occurs, they all agree the issue is significant.

"Empathy is an incredibly important feeling," says Antonio Damasio, head of neurology at the University of Iowa Medical Center and author most recently of *Looking for Spinoza: Joy, Sorrow and the Feeling Brain*. "Without compassion and empathy, it's hard to imagine human relations or the construction of a normal society."

In studying empathy, "neuroscientists are now going for the motherlode, the seat of understanding others," says Andrew Meltzoff, co-director of the Center for Mind, Brain and Learning at the University of Washington in

(Continued on page 2)



I feel you! Our ability to empathize sets us apart from other animals, but understanding the brain mechanisms behind empathy has proved challenging.

EMPATHY, continued from page 1)

Seattle and a coauthor of *The Scientist in the Crib*. "I know of no question more exciting, or in today's world more important."

Clues Accumulate

Current insights into empathy build on nearly 40 years of clues about the nature of facial expressions of emotion and the human ability to imitate someone else.

Paul Ekman, a psychologist at the University of California, San Francisco and author most recently of *Emotions Revealed*, began his pioneering studies on facial expressions in 1965, when the conventional wisdom held that they were learned and culturally specific. In a series of studies, including one that involved a tribe in New Guinea who had little contact with outsiders, Ekman proved otherwise—that facial expressions of emotion are understood around the world. This confirmed what 19th century evolutionary biologist Charles Darwin first proposed: that such expressions relate to universal expressions of emotion and are probably innate. Subsequent research by Ekman and others has shown that facial expressions enhance the internal experience of emotion: frown and you feel sad; smile and you feel happy.

Other researchers debunked the once-conventional wisdom that mimicry was learned and showed that it was innate. In the 1970s and 1980s, Meltzoff and colleagues found that 12- to 21-day-old infants could imitate four distinct adult gestures such as sticking out their tongues and opening their mouths. Even newborns less than an hour old engage in rudimentary forms of imitation.

Studies in the 1990s concluded that both mimicry and facial expressions of emotion could occur unconsciously, indicating that some automatic brain process was involved. Using electrodes to measure electrical activity in relevant muscles, the psychologist Ulf Dimberg and colleagues at Uppsala University in Sweden found that people unconsciously react to pictures of happy and angry faces by making similar facial expressions—even when instructed to remain neutral or to do the opposite, such as frown in response to a smile. Tanya Chartrand and John Bargh at New York University described a "chameleon effect" in which people unconsciously mimic both facial expressions and mannerisms when interacting with others. The more empathetic the person, the more he or she unconsciously mimicked another person's behavior.

The brain processes underlying both interpretation and mimicking of facial expressions remained unclear. A crucial clue was provided by the mid-1990s discovery of "mirror neurons" in monkeys, by Giacomo Rizzolatti and colleagues at the University of Parma in Italy. Such mirror neurons become active in a monkey's brain whether the animal is performing a particular action or merely observing it in another monkey. In subsequent research, Rizzolatti proposed that a similar "mirror system" in people might explain how people understand and imitate other people's gestures.

Neuroscientists posed another question: could this mirror system somehow be involved in empathy?

"In many ways the current view is counterintuitive: we don't smile because we share someone's joy; we share the joy—at least in part—because we are smiling."

A New Paradigm

In answering that question—thanks in large part to brain imaging techniques—researchers have developed a new paradigm about empathy. In many ways the current view is counterintuitive: we don't smile because we share someone's joy; we share the joy—at least in part—because we are smiling.

Damasio is probably the best-known proponent of this way of thinking about emotions and feelings. In Damasio's view, mirror neurons and other body-sensing areas of the brain constitute a type of theater. Empathy involves a brain simulation in these theaters, so that one person's emotions and feelings play out in an observer's body and mind—as if generated by the observer himself.

Two recent papers suggest that imitation is key to the process. In a study published in March in the *Philosophical Transactions of the Royal Society of London-Biological Sciences,* Meltzoff and Jean Decety, an internationally known expert in neuroimaging, propose a three-phase developmental process that begins with imitation and culminates in empathy.

During the first phase, newborns mimic adults, demonstrating an innate ability to make connections between

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The Neuroscience Newsletter

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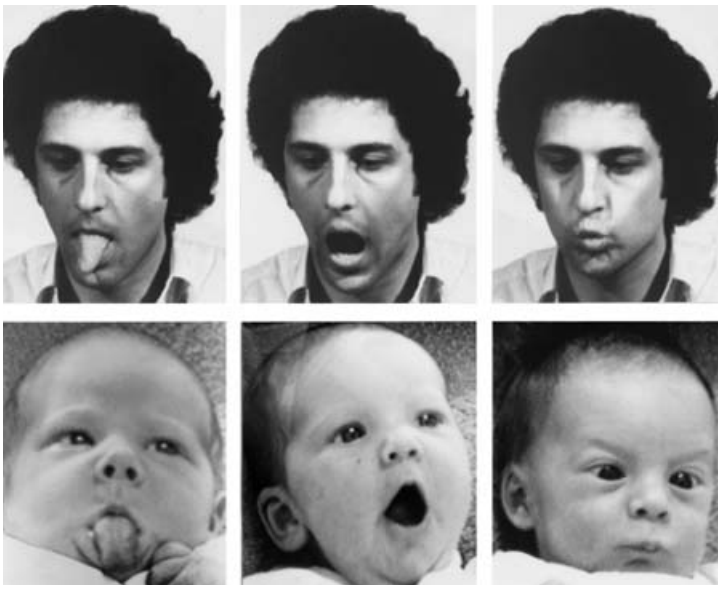
their own actions and those observed in others. The next step occurs as infants use proprioception (the ability to sense muscle movement and tension) to associate certain facial expressions with particular emotions. Muscle movements that create a smile, for instance, become associated with joy. The final step toward empathy occurs when children notice that other people make the same expressions they do, and infer that other people must feel the same way the child himself does when making that expression.

The process takes about two to three years: a toddler who hugs a crying playmate is probably showing the first signs of empathy. "We think empathy is a developmental outcome of the baby recognizing similarities between the self and others," a process that begins with imitation, Meltzoff says.

Further support for this theory is provided in an April paper in the *Proceedings of the National Academy of Sciences*. Marco Iacoboni and colleagues at the University of California, Los Angeles describe a brain circuit that may underlie empathy. Using functional MRI, the researchers identified a circuit that extends from areas in the cerebral cortex that are critical for executing and representing actions (similar to the "mirror system" identified in monkeys) to areas in the limbic system that process emotions. The executive and emotional sections of the circuit are linked by the insula, an area within the cortex.



Twelve- to 21-day-old infants imitate adult facial actions, indicating that infants are innately "connected" to others from birth. Imitation may lay the foundation for feeling empathy later on.

The researchers found that this brain circuit is activated whether someone merely observes facial expressions of emotion or actively imitates them—but that imitation significantly heightens activity in the circuit (and presumably the intensity of emotions). "Our findings show for the first time how reflexive facial expressions prompt our brain to heighten empathy for the feelings of someone else," Iacoboni says. "We think this is the neurobiological mechanism that might explain what has been observed behaviorally" in other studies.

Chicken/Egg Question

Debate continues about which comes first, imitation or empathy—or even if one is required for the other.

"Facial expressions are very important" for empathy, Damasio says, but are not the whole story. "A person experiences a feeling not only because he imitates facial expression but also because of visceral changes" such as increased heart rate.

"I don't think we know whether imitation is required to understand expression or is an empathetic response to observed emotion," Ekman says, noting that people with Moebius syndrome, a rare disorder that causes facial paralysis, "can't make facial expressions, but they have no problem recognizing and interpreting emotions." What's more, emotion can be triggered in milliseconds, he says, and "we don't yet have the tools to provide that time resolution when observing changes in the brain."

Other unanswered questions include whether gender differences exist in empathy, and how different types of empathy (emotional, cognitive, and compassionate) are processed in the brain. Answering such questions may raise new ones.

"We are at the beginning of a new wave of research in neuroscience," Meltzoff predicts.

Ann MacDonald writes about science and medicine from Wakefield, R.I.

Regenerative Medicine:
Turning Science Fiction Into Fact

BY BRENDA PATOINE

Restoring lost brain function with cells grown in a dish. Mobilizing bone marrow cells to act as stand-ins for damaged neurons. Using chemical cocktails to induce nerve fibers to grow and bridge a spinal cord injury.

What sounded like science fiction not too long ago is now squarely in the realm of possibility—even reality—as neuroscience embraces the "new" science of regenerative medicine. Fueled by the hope (or, some would say, hype) that stem cells may have the capacity to rebuild virtually any damaged or diseased tissue in the body, regenerative medicine has become somewhat of a buzzword in science circles. But what are the real, short-term prospects of this seemingly futuristic branch of medicine, and what will it take to make "brain regeneration" a reality?

"Regenerative medicine has been practiced since the early '70s," says Irving Weissman, a Stanford University biologist who has pioneered techniques for regenerating blood cells destroyed by cancer treatments. "That's the most direct demonstration" of regenerative medicine, Weissman says. "All the rest is a dream. It's easy to say the dream, but it's harder to make it work."

Changing Fate

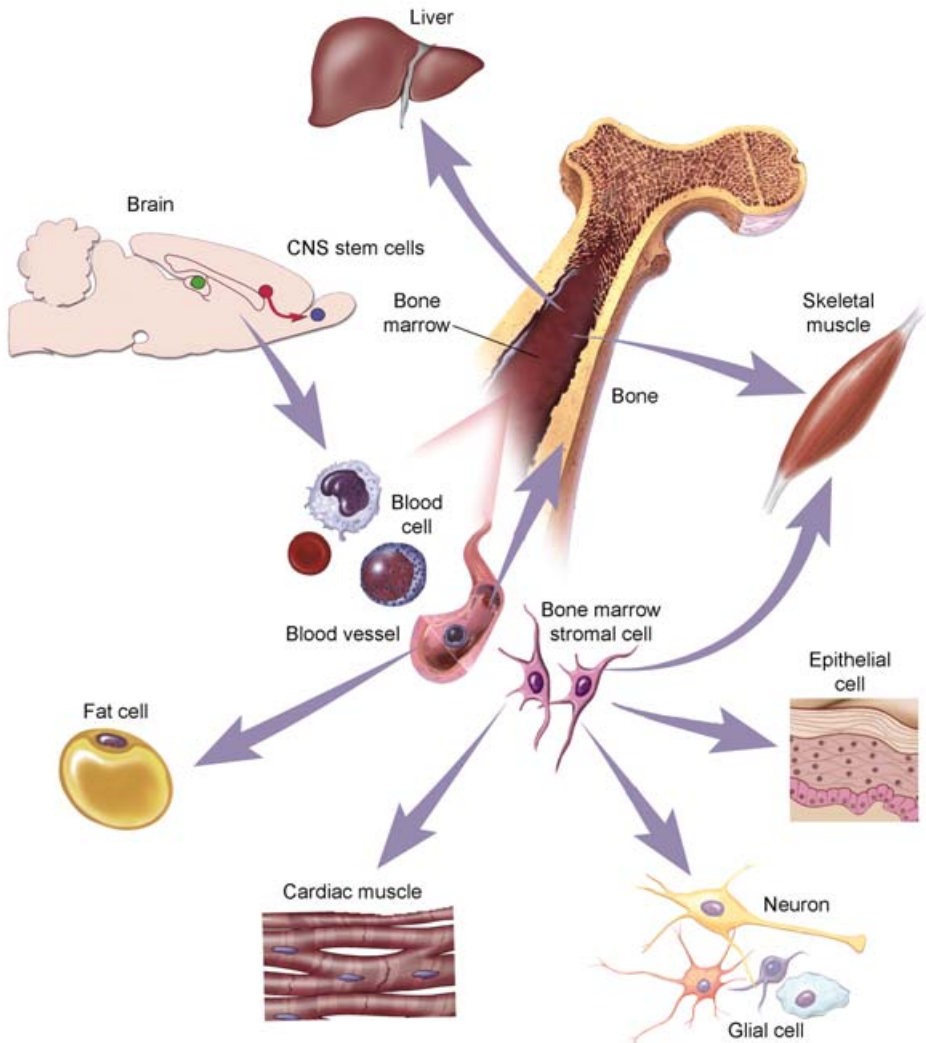
One of the biggest hurdles to making "the dream" a reality is understanding the signals and biochemicals that dictate what type of tissue a stem cell will develop into. While stem cells derived from days-old embryos have the potential to become any cell type in the body, so-called "adult" stem cells appear to be more limited—they tend to develop only into cells specific to the organ in which they're found. But a growing number of scientific reports suggest that stem cells can "change fate" under certain conditions—a feat that would potentially make it easier to mass produce the types of cells needed for regenerative therapy. Recent articles in leading science journals have shown, for example, that bone marrow cells can become neurons, or that muscle stem cells can develop into blood cells. But the evidence for such fate changes is preliminary and is often met with skepticism by the cognoscenti of the field.

"These [purported fate changes] sound absolutely fantastic, and I think in some cases they are exactly the way they're portrayed," says Ron McKay, a stem cell expert with the National Institute for Neurological Disorders & Stroke. "But sometimes you're fooled, and what you think is a fate change is actually some other kind of event." For example, McKay says that sometimes two cells fuse together and give the impression that a cell has transformed when in fact it has not.

"It's quite complicated research," says McKay. "We're definitely making progress, but there's a lot of stuff we need to understand." While stem-cell based regenerative medicine is without question one of the most promising areas in all of medical research, McKay says, "We're talking about a clinical domain that is full of unknown questions. We should be careful when we think about the clinical applications."

Pinning Hopes on Stem Cells

One of the biggest hopes for applying stem-cell based therapies to neurological disease is in Parkinson's disease research. In Parkinson's, a discrete group of nerve cells (those that pro-



Scientific reports suggest that adult stem cells may be able to "change fate," or develop into cells of organs other than the ones in which they are found. Some experts are skeptical.

duce the neurotransmitter dopamine) in a particular brain region die off, making the disease potentially amenable to treatment with transplanted cells that might assume the function of cells lost to disease. In fact, a total of about 300 patients worldwide have already been treated with so-called cell transplant therapy, which uses tissue extracted from aborted fetuses—a much different process than generating new tissue from stem cells. While individual patients have improved dramatically with this treatment, results overall have been inconsistent, and a number of treated patients developed severe dyskinesias, uncontrollable movements that appear to be related to the specific placement in the brain of the tissue graft. In the first controlled clinical trial of the therapy, about 15 percent of patients experienced unacceptable side effects. Continued investigations of patients who have undergone the transplants is helping shed light on what went wrong and why, so the procedure can be adjusted as necessary.

Clearly, additional research is critical to further developing the cell-transplant approach as a viable regenerative treatment for Parkinson's. Yet additional research is hampered not only by the ethical issues raised by the use of fetal tissue, but also by practical issues related to the quantity and quality of the cells that are obtained. A total of six donors are needed within a closely defined time period, which means tissue is often variable and may be contaminated or fragmented. This makes it difficult to standardize or optimize the transplant, critical steps in developing the therapy. Not surprisingly, the cell-transplant field has looked to stem cells as one potential solution to these problems.

"For the next step [in cell transplant research for Parkinson's], it is essential to move in the direction of generating cells specifically for transplantation purposes," says Anders Bjorklund, a neuroscientist with the University of Lund, Sweden, who has pioneered neural transplantation techniques. Moving to the next step, which is to develop "a very well-controlled, standardized transplant procedure with limited or little variability," depends upon "access to another source of cells that are more standardized and are available in larger numbers" than the fetal cells, he says.

Dozens of research groups worldwide are racing to develop clinically viable stem cells to fulfill the urgent need for "another source of cells," not only for use in Parkinson's disease, but in Huntington's and amyotrophic lateral sclerosis (ALS) as well. Many different strategies are being pursued, including using stem cells as a means to deliver growth factors that nourish and support target cell populations. Clive Svendsen and colleagues at the University of Wisconsin-Madison are using this approach (see sidebar), which Svendsen predicts "might be the first clinical use for stem cells" as a means of stopping or reversing cell death in neurodegenerative disease.

Lessons from Gene Therapy

While Bjorklund, like other experts, sees promise for using stem cells to overcome the barriers to optimizing cell transplant procedures, he cautions that there is a "risk to oversell the benefits" of stem cell therapy. "We need time to develop knowledge and technology properly before we proceed to try it" as clinical treatment.

He points to the gene therapy field as evidence of the inherent risks in moving too quickly into human clinical

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GROWTH FACTORS SHOW PROMISE FOR PARKINSON'S

With stem cell therapy not yet ready for clinical use, and fetal-cell transplantation on hold until safety issues can be sorted out, the Parkinson's field is looking for other ways to regenerate lost dopamine. They may have found a viable candidate in GDNF (glial cell-line derived neurotrophic factor), a naturally occurring growth factor that seems to be critical to the development and maintenance of dopamine nerve cells.

In May, a group of researchers led by Stephen S. Gill of Frenchay Hospital in Bristol, U.K., reported promising early results from five Parkinson's patients in whom GDNF was infused into a specific part of the brain via an implanted catheter. The study, published in *Nature Medicine*, reported no significant side effects of the treatment, and all five patients showed some improvement in movement and in activities of daily living. There was also a 64 percent reduction in involuntary movements (dyskinesias) among the four patients who experienced these problems as a result of previous treatment with levodopa, the mainstay of drug therapy for Parkinson's.

Because it was designed to assess safety, the study was "open-label," meaning there was no control group that received a placebo, or inert treatment. "This was a very well-done trial," says Jeffrey Kordower, a neuroscientist at Rush-Presbyterian Medical Center in Chicago who is studying GDNF-based gene therapy for Parkinson's. "However, we have to be very cautious of open-label studies. There are now multiple examples of studies of similar design where effects of the same size seen in this study have failed to yield significant results in double-blind trials." (Double-blind studies incorporate a placebo, and neither the patients nor the researchers know which patients are receiving "active" therapy and which are receiving the placebo.) Amgen, a biotech company that holds the patent for GDNF, is initiating a double-blind study to investigate GDNF implants; those results will be important to determining the viability of the approach.

There have been previous attempts to use GDNF in Parkinson's patients, but the Gill study is the first time it has been infused directly into the putamen, a small nucleus of cells within a region of the brain that controls complex movements. Other scientists, including Kordower's group, are using a killed virus that has been genetically engineered to secrete GDNF as a vector to deliver the growth factor, but this approach is still in preclinical stages. University of Wisconsin-Madison researcher Clive Svendsen, a co-author of the Gill paper, is investigating the use of stem cells as a delivery vehicle for GDNF, a strategy he says "removes the problem of direct virus delivery to the brain." One key challenge in this endeavor, he says, is to "prove constant release of GDNF following transplantation" of the cells, and those studies are currently under way.

—B.P.

Who's In Charge Here?

Orchestrating Sleep and Waking in the Brain

BY HAKON HEIMER

There you are...on vacation. No alarm clocks or schedules. You'll do whatever you like, whenever it suits you. Yet each morning you wake up around the same time. Alert until the afternoon, you then feel the urge to nap, though you wake up after only a few hours. You'll enjoy a few hours of evening alertness, before you drift off to the land of Nod for a prolonged sleep.

This cycling is written in a schedule more fundamental than your daily minder—one imposed by the brain systems that orchestrate sleep and waking.

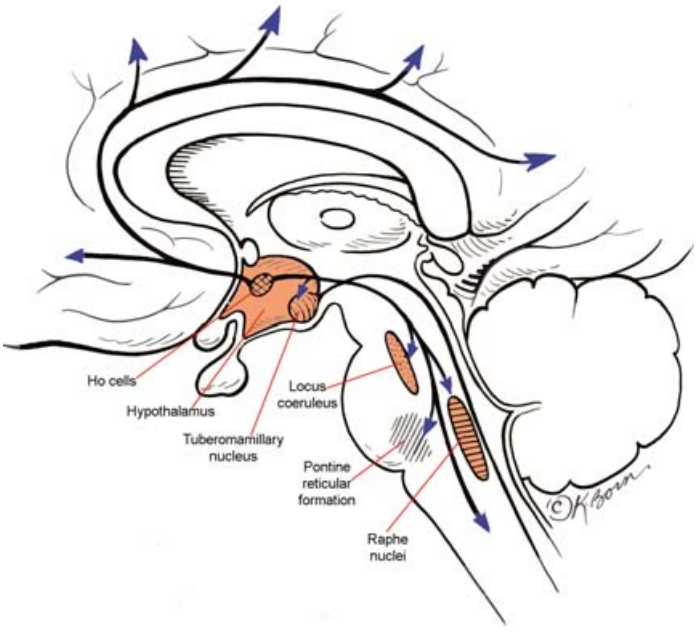
For most of the last century, the dominant paradigm held that during waking hours you accumulated mysterious sleep "factors," probably biochemicals of some sort. When a threshold was reached, the sleep factors put you to sleep. The sleep factors were broken down during sleep, and eventually you were allowed to wake up. Sleep was in charge, wakefulness had to toe the line.

As with most brain functions, the situation has turned out to be vastly more complicated. There is indeed a sleep debt that accumulates, but there are also systems that actively promote wakefulness. The most fundamental is the circadian clock, a group of neurons in the hypothalamus. The clock employs a set of genes that turn on and off in complex patterns to create a 24-hour cycle, uninfluenced by how much sleep we get. And there is accumulating evidence that two other cell groups of the hypothalamus—one that promotes wakefulness and one that promotes sleep—are poised to translate the clock's rhythms to other brain areas.

Stay awake!

The most important recent advance in sleep research was the discovery that narcolepsy patients can blame their inability to stay awake on the malfunction of a neuronal signaling peptide called alternately hypocretin or orexin (by the two research groups that reported this independently in 1999). The neurons that produce the peptide in the hypothalamus have been studied intensively in the past few years, and it has become clear that they are well situated—and connected—to be intermediaries that help impose the circadian clock's rhythm on the rest of the brain.

Emmanuel Mignot, M.D., Ph.D., and his colleagues of Stanford University, one of the groups that identified



Most narcoleptics have lost cells for a peptide called hypocretin or orexin, which is produced in the hypothalamus. This discovery marked an important advance in sleep research; hypocretin/orexin may play a role in normal sleep-wakefulness cycles.

the role of hypocretin/orexin in narcolepsy, are trying to determine whether the peptide plays a role in the normal regulation of wakefulness. In a recent article in the *Journal of Neuroscience*, they measured the fluctuations of hypocretin/orexin in the brains of squirrel monkeys over the course of sleep and waking.

During the early morning hours, hypocretin/orexin levels remained low, indicating that the peptide is not a wake-up signal. Late in the day, however, levels of hypocretin/orexin increased. The authors suggest that the peptide is actively working to maintain alertness as the sleep debt accumulates, perhaps even in response to the sleep debt.

"To be sure that this is true, we would like to figure out if these fluctuations are driven by the circadian clock, the accumulating sleep debt, or both. I suspect it is both," said Mignot.

You're getting sleepy...

What about the other side of the equation—the sleep factors? Of the more than 50 biochemicals that can induce sleep, only a handful are strong candidates for a role in normal sleep, says James Krueger, Ph.D., of Washington State University.

"Among the sleep substances with the best evidence for a role in regulating normal sleep/wake schedules is GHRH—growth hormone releasing hormone," says Krueger. As its name implies, GHRH stimulates the release of growth hormone (GH), which occurs during non-rapid-eye-movement (non-REM) sleep, the deep sleep phase during which we do not dream. GH uses this time to help replenish tissues such as muscle and bone. However, GHRH and GH probably also play roles in regulating sleep states, and they may do this by acting, independently, on separate brain circuits.

In the January issue of the *American Journal of Physiology*, Krueger and his colleagues reported that mice genetically engineered to have faulty GHRH function do not sleep as much as their non-mutant counterparts. When the researchers bypassed the GHRH system to add GH directly, they discovered that REM sleep—a phase characterized by dreaming and

high brain activity—returned to normal, but the non-REM sleep did not.

"This is a nice demonstration that GH apparently promotes REM sleep, whereas GHRH promotes non-REM sleep," says Krueger.

Dueling maestros in the hypothalamus?

Krueger's group and other researchers have found evidence that GHRH influences sleep in a third area of the hypothalamus—the preoptic anterior hypothalamus (POAH). Whereas hypocretin/orexin neurons are active during waking hours, these POAH neurons are active only during sleep. When GHRH is applied directly to the sleep-active neurons, excess non-REM sleep is induced.

These findings have led to the suggestion that the hypocretin/orexin and POAH neurons are twin conductors, interpreting the cycles of the circadian clock for an orchestra of brain areas attuned to both of their batons. One important bit of evidence is that each area sends nerve projections to the "ascending arousal system"—small groups of neurons deep in the brain that have long been known to "wake up" the rest of the brain. The hypocretin/orexin cells activate the arousal system, whereas POAH input inhibits it.

Mignot believes there is enough evidence to draw a speculative flow-chart of the circadian clock directly or indirectly driving these neuronal groups, which in turn drive other sleep/wake areas. The same is not true for the other big input to the equation—sleep debt. "I think the biggest mystery right now is still the sleep debt—what the neurochemical nature of it is, and how that, in turn, influences structures important for expressing sleep and wake," says Mignot.

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

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FROM THE FRONTIER

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cluster of risk factors at the follow-up. Two conditions in particular—obesity, as measured by a high body-mass index, and insulin resistance—were the chief culprits: Subjects with the highest values scored strikingly higher on hostility tests than did those with the lowest. The study appeared in the May issue of *Health Psychology*.

"Most parents are aware that their kids need to exercise and eat right," says study author Kristen Salomon, now at the University of South Florida. "But they need to be aware of the psychological issues as well." Salomon notes that although overweight youngsters may become hostile because of the way they're treated, "In our study hostility actually preceded the biological factors." She adds that interventions designed to reduce hostility may also prevent heart disease as well as its precursors, obesity and type-II diabetes, which are significant health concerns in themselves.

••• **"Smart" virus eradicates malignant brain tumor in mice.** A custom-designed version of the common cold virus has proved strikingly successful against a brain cancer known as glioblastoma multiforme (GBM). In the May 7 issue of the *Journal of the National Cancer Institute*, neurologist Juan Fueyo of the University of Texas M.D. Anderson Cancer Center, along with colleagues at the University of Alabama at Birmingham and the Institut Catala d'Oncologia in Barcelona, Spain, reported that when mice were treated with the redesigned virus, more than half were symptom-free after 100 days—considered clinically cured—whereas untreated mice died after 20 to 30 days. Microscopic examination of the treated mice revealed only calcium-filled scars where the tumors had been, with no sign of either tumor or virus.

GBMs are notoriously difficult to treat; even with surgery, radiation, and chemotherapy, the prognosis for survival is only about two years. To devise therapies against this tumor, Fueyo's team and others have worked with a genetically engineered adenovirus since the early 1990s. The viral "smart bomb" takes advantage of the fact that in cancerous cells, the so-called retinoblastoma (Rb) protein malfunctions. In normal cells, Rb acts as a brake on cell division; it also prevents viruses from replicating inside the cell. Cancerous cells without functional Rb cannot defend themselves against the adenovirus, which kills each cell by replicating itself.

To ensure that the virus leaves healthy cells alone, Fueyo and colleagues disabled a key protein known as E1 A, which the adenovirus uses to disarm a normal cell's Rb protein, resulting in a cancer-specific virus. The most recent version of the virus, dubbed Delta-24-RGD, is more successful than its predecessors at infecting large numbers of cells, creating what Fueyo calls "a wave of anticancer effect all the way to the periphery of the tumor."

Fueyo notes that surgery to introduce the treatment directly into the tumor would be less invasive than that which brain cancer patients currently undergo, and because glioblastoma multiforme does not spread to other parts of the body, one treatment should suffice. The National Cancer Institute is now producing Delta-24-RGD in a form pure enough for clinical use; when this supply is available, the virus will be tested for toxicity in animals, and clinical trials in humans may begin in as little as one year.

••• **Fatty acid "switch" may be food intake sensor.** The urge to eat originates not in the stomach, but in a part of the brain called the hypothalamus. This structure keeps tabs on the supply of nutrients in the bloodstream, making the appropriate adjustments to what scientists call "feeding behavior." Now, researchers from the Albert Einstein College of Medicine, New York, and Sigma Tau Pharmaceutical Industries, Pomezia, Italy, have isolated a key step in the process.

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(REGENERATIVE, continued from page 5)

trials. Experimental gene therapy research has come under fire after the deaths of several patients enrolled in clinical trials and after two children developed leukemia while part of a French study that used a retrovirus to deliver a gene product. Although the reasons for the deaths and the cause of the cancer are still under investigation, the results have cast a shadow over the field. "We should all learn from their experience," Bjorklund says. "Any short-term gains from going into the clinic may have a high price in that they could result in setbacks for the whole field."

"Taking any technology in molecular and cell biology to the clinic is a major endeavor," says McKay. "I'm not saying this is simple, but it's going to happen....One step at a time."

Brenda Patoine is a medical and science writer based in LaGrangeville, N.Y.

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Luciano Rossetti and colleagues suspected that neurons in the hypothalamus contained a "sensor" linked to the metabolism of fatty acids within the cell. In the current study, reported in the June issue of *Nature Medicine*, the team zeroed in on an enzyme called carnitine palmitoyltransferase-1 (CPT1), which plays a role in fatty acid metabolism. When this enzyme was inhibited in the brains of rats, either genetically with a construct called a plasmid or pharmaceutically, the effects were immediate: The rats ate less, and less glucose was released from the liver.

The researchers surmise that with the action of CPT1 switched off, the increased fatty acid activity in select neurons of the hypothalamus sent a signal of "nutrient abundance," in other words, telling the brain that the rat wasn't hungry. The resulting twofold effect—decreasing nutrient availability both from the outside (as food) and from the inside (in the form of glucose production)—has important implications. In type-II diabetes, for example, excess blood sugar sets up a vicious circle: The body becomes resistant to its own insulin (a hormone that helps glucose get into the body's cells), which ratchets levels of blood glucose even higher. A therapy that not only decreases appetite but reins in the liver's release of glucose into the bloodstream could treat both obesity and type-II diabetes, a condition for which obesity is a risk factor.

"News" is written by Elizabeth Norton Lasley, a freelance science writer in Woodbury, Conn.

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