THE DANA FOUNDATION'S

BRAINWORK

The Neuroscience Newsletter

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News FROM THE FRONTIER

••• **ATP adds insult to spinal cord injury.** A study published in the August *Nature Medicine* reveals a startling new role for adenosine triphosphate (ATP), the chemical compound that supplies energy for many biochemical processes in living cells. Under certain circumstances, ATP can inflict great damage on the very cells that it normally supports.

Scientists at the University of Rochester, led by neurosurgery professor Maiken Nedergaard and colleague Xiaohai Wang, found in an animal model that when the spinal cord is injured, a series of chemical signals releases a flood of ATP at the site of the injury. Excessive levels of ATP prove fatal to motor neurons in the surrounding area, and the large-scale loss of motor neurons in turn brings on the paralysis that is all too often associated with spinal cord injury.

However, when the scientists used experimental compounds to block the effects of ATP at the injury site, the animals showed much lower rates of motor neuron death and significantly

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Neurogenesis Holds Promise as Treatment for Brain Disease and Injury

BY SCOTT P. EDWARDS

In the early 1960s, an MIT scientist made a discovery that stood science on its head. Finding evidence that new cells are produced in the hippocampus of the adult rat brain, Joseph Altman turned upside-down the longstanding belief that animals are born with all the neurons they are ever going to have. In 1988, scientists showed that the adult human brain produces new neurons as well. These and other findings since hold great promise for treating brain injuries and neurodegenerative diseases.

Neurogenesis is the process by which primitive cells become neurons and then fully develop into mature neurons with all their appropriate connections. Neurons are born in regions of the brain that have many neural precursor cells. These precursors, or stem cells, can generate either neurons (the information connection for the brain and the rest of the nervous system) or glia (the glue that holds neurons together).

After a neuron is generated, it migrates within the brain and differentiates into a sensory neuron, a motor neuron, or an interneuron, all of which send and receive specific neurotransmitters. As the brain develops, molecular signals from other cells help determine a neuron's shape and location, the type of neurotransmitters it will produce, and the neurons to which it will connect. These neural circuits, connecting neuron to neuron, remain in place throughout adulthood.

The birth of new neurons, such as the motor neuron shown here, is called neurogenesis. Researchers have found that neurogenesis takes place in the adult brain, which may have implications for treatment of brain injuries and disease.

While neurons are among the longest-living cells in the body, some die unnaturally, as occurs in Alzheimer's, Huntington's, and Parkinson's diseases, among others.

A Neuroscience Controversy

While some neuroscientists consider neurogenesis in the adult brain an unproven theory, it is generally well accepted that new neurons are born in two specific areas of the brain: the hippocampus, which is involved with learning and the acquisition of new memory, and the olfactory bulb, which is responsible for the sense of smell.

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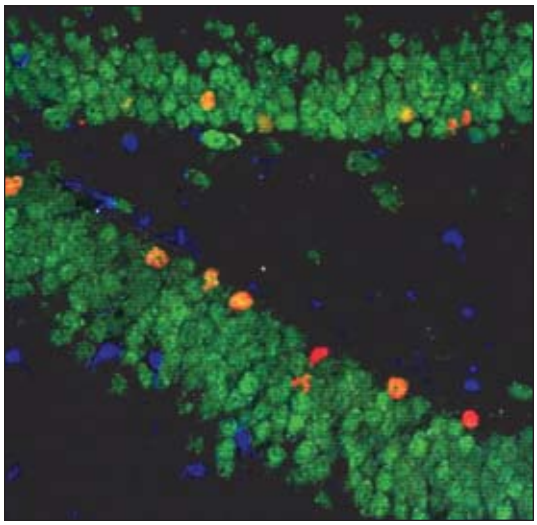
(NEUROGENESIS, continued from page 1)

In 1999, a team of scientists at Princeton University led by psychologist Elizabeth Gould found in monkeys that the formation of new neurons also takes place in several regions of the cerebral cortex (also called the neocortex), a complex region of the brain that is responsible for executive decisionmaking, short-term memory, visual recognition of objects, and the representation of objects in space.

"When adult neurogenesis was 'rediscovered' by many groups, it was finally accepted for the hippocampus and olfactory bulb, but not for the neocortex," says Gould. There are probably several reasons researchers reject neurogenesis in the neocortex, she adds, including conflicting data reported by different research teams, a lower level of new neuron production than occurs in either the hippocampus or the olfactory bulb, and difficulty detecting neurons in the neocortex.



This image from the dentate gyrus in a mouse's brain shows mature neurons in green and newborn cells in red. The mouse had just spent 40 days running on a wheel; exercise encourages neurogenesis. The blue cells are glial cells.

There are reports of neurogenesis in other areas of the brain, including the substantia nigra, olfactory tubercle, amygdala, and striatum, says Gould, but the level of neuron addition in these areas seems to be quite low and there is no consensus among neuroscientists about whether evidence supports these claims.

Inducers and Suppressors

Extensive research has been conducted to determine what might induce or suppress neurogenesis. Among the candidates are exercise; stress, depression, and chronic administration of antidepressant medications; hormones; and nonsteroidal anti-inflammatory drugs.

Recent research shows that exercise may contribute to the formation of new connections among nerve cells, as well as to the growth of neurons. Although researchers are not sure why, it is possible that the release of endorphins when one exercises induces the growth of new neurons in the hippocampus—or that this type of exercise might simply supply more blood to the brain, giving new life to neural cells.

"Exercise potently increases neurogenesis," says Theo D. Palmer of the Stanford University School of Medicine. "It changes the local environment of stem cells, causing growth factors to act on neural precursor cells to make new neurons and create changes in the brain's circuitry."

While exercise can induce neurogenesis, stress can dramatically suppress new neuron production. Studies have shown that both physical and psychosocial stress reduce the proliferation of neural precursor cells in the dentate gyrus region of the hippocampus. Patients with depression or post-traumatic stress disorder have reduced hippocampal volume. Given the relationship between stress and neurogenesis, scientists believe that reduced adult hippocampal cell proliferation or neurogenesis may be involved in the pathophysiology of depression.

Stress has long been known either to cause depression or worsen its symptoms, says Ronald Duman, who studies the effects of stress, depression, and antidepressant therapy on neurogenesis in his lab at Yale University.

Duman found that chronic treatment with antidepressants encourages neurogenesis in "clinically depressed" experimental animals. "We've also found that antidepressant treatment can block or reverse the down-regulation of neurogenesis that is caused by stress," he says. He and his colleagues have identified certain transcription factors and signaling pathways involved in neurogenesis and are examining how different antidepressants might induce neurogenesis.

Gould, the Princeton psychologist, has shown that glucocorticoids (stress hormones) decrease adult neurogenesis in the hippocampus. Stressful experiences, she says, can decrease neurogenesis by elevating stress hormone levels. She recently reported that even stressful experiences during brain development can decrease neurogenesis in adulthood by making animals hypersensitive to glucocorticoids.

"On the other hand, estrogen has been shown to enhance adult neurogenesis in the hippocampus," Gould says. "Prolactin [a protein hormone produced by the pituitary gland to induce and maintain lactation] also stimulates adult neurogenesis in the olfactory bulb." Because prolactin rises with pregnancy, pregnancy itself is also

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associated with an increase in new neuron formation, she adds.

While studying the effects of radiation therapy on patients with head and neck cancers, Stanford researchers found that the side effects of radiation treatment often rob patients of memory and other critical cognitive functions. Working with rats, Michelle Monje showed that cranial irradiation interferes with neurogenesis by altering the environment surrounding cells in the hippocampus. She and Theo Palmer determined that inflammation might be responsible for this decline in neural cell replacement in these cancer patients.

"Inflammation caused by injury or disease changes progenitor cells into glia, not neurons," says Palmer. "Our study showed that the [brain] cancer is cured in patients who are receiving radiation therapy, but that progenitor cells that make neurons are killed off along with the cancer cells."

In a recent study, Monje observed that local inflammation caused by cranial irradiation inhibits neurogenesis in the hippocampus and that the administration of common nonsteroidal anti-inflammatory drugs, such as indomethacin, can restore some neural cell replacement.

Neurogenesis as Therapy

While Palmer considers the therapeutic potential of neurogensis to be "all very speculative," a number of neurodegenerative diseases and other conditions, including Huntington's disease, Alzheimer's, and depression, might be candidates for cell replacement therapies.

A recent study at the University of Auckland in New Zealand found, in postmortem brain tissue of Huntington's disease patients, that neurogenesis occurred in the subependymal layer (SEL) of the brain. This area is adjacent to caudate nucleus, the region most affected by Huntington's. In early neural development, cells migrate from the SEL to form the caudate nucleus. The researchers say their findings suggest that these newborn neurons are migrating toward the caudate nucleus to replace cells killed by Huntington's disease. Treatments for neurodegenerative diseases could be augmented with growth factors and drugs that have been shown to induce neurogenesis, they add.

Neurogenesis may also be helpful in treating Alzheimer's disease. Researchers working with mice are focusing on the Presenilin-1 (PS1) gene, found in both mice and humans, which mutates in early-onset Alzheimer's. PS1 encodes a protein in hippocampal cells and other regions of the brain that are associated with memory and learning.

After deleting the gene from mice, the researchers put the mice in an environment in which they were subjected to a number of memory and learning tests. They found that mice with the deleted PS1 gene formed fewer nerve cells after being stimulated, suggesting that PS1 is involved in neurogenesis. Initially, these mice recalled more information but had difficulty forming long-term memories, which also occurs in early-stage Alzheimer's.

Meanwhile, Ron Duman's work at Yale has implications for the development of new antidepressants and treatments for depression. He is conducting studies to identify and characterize the factors and pathways that control neurogenesis. "The goal is to develop better treatments that are faster-acting and more effective," he says. "Our studies will provide information for the design and development of novel approaches to regulate neurogenesis and possibly for the treatment of depression."

Other research focuses on whether neurogenesis could treat brain injuries, Parkinson's disease, and mood disorders. Harvesting neural stem cells and transplanting them to specific areas of the brain to replace endogenous cells is another topic of study.

Although recent discoveries of neurogenesis in the adult human brain have given scientists new insight into how our brains work and could possibly lead to therapies for a variety of diseases, Theo Palmer sounds a word of caution: "Clearly, there's an advantage for mammals to have a brain that regenerates. But, we don't yet know what that advantage is."

Scott P. Edwards is a freelance medical writer based in Holliston, Mass.

Atypical Antipsychotics May Lower Violence

BY MAIA SZALAVITZ

Schizophrenia is probably the most stigmatized mental illness—largely because many people associate it with violence. Although an overwhelming majority of violent crimes have nothing to do with schizophrenia—and although the vast majority of people with schizophrenia never physically harm anyone—studies have found that people with schizophrenia are about four times more likely to be violent than those who do not suffer from this mental illness. Until recently, there has been little success either at predicting or at preventing violence in people with schizophrenia.

Recent research suggests, however, that the atypical antipsychotic medications introduced into schizophrenia treatment beginning in the late 1980s, such as clozapine and risperidone, may significantly curb aggression. Statistics on usage rates are ambiguous, but if these findings are confirmed, wider use of these drugs—which are considerably more expensive than older medications such as haloperidol and trifluoperazine—not only could help cut crime and associated costs, but also might help reduce the social stigma surrounding schizophrenia. The research may also offer hints about the chemistry of violence in the brain and insights about addiction.

A new study, published by Duke University researchers Jeffrey Swanson, Marvin Swartz, and Eric Elbogen in a recent issue of *Schizophrenia Bulletin*, found that people who consistently took the newer medications had half as many violent incidents as those who regularly took the older drugs.

"The effect is very substantial," says Marvin Swartz, professor of psychiatry at Duke University Medical School and co-author of the study, explaining that the new drugs looked even better

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(VIOLENCE, continued from page 3)

when compared with no medications at all, reducing violence by 75 percent. Violence was defined as physical assault intended to harm and was measured by reviews of medical records, arrest reports, and accounts from patients themselves.

"I think it is very suggestive and consistent with a lot of other evidence that these drugs reduce violence," says Herbert Meltzer, professor of psychiatry at Vanderbilt University Medical School. The only problem with the study, Meltzer says, was that patients weren't randomly assigned to medications. As a result, pre-existing characteristics unknown to the authors could have caused less violent people to be given the newer medications, giving a false impression of violence reduction. However, according to the study, the researchers did numerous statistical analyses to try to find such influences and did not discover any.

Research suggests that newer medications for schizophrenia, here depicted to indicate the disorder in cognition, may reduce rates of violence.

A consistent problem in schizophrenia treatment is that patients often refuse antipsychotic medications or stop taking them—but the new antipsychotics offer hope here, too. One of the most important reasons people with schizophrenia avoid the older drugs is unpleasant side effects such as drooling, a shuffling gait, and difficulties with movement that can be permanent, even if the drug is stopped. These side effects seem to be related to the action of the drugs on the brain's dopamine system—especially certain D2 receptors.

The newer drugs also affect dopamine, but they have critical effects on serotonin system, particularly the 5HT2A receptor, which is plentiful in areas that control memory and mood. Meltzer's research suggests that it is the strong effect on this serotonin receptor and possibly others, combined with weaker dopamine-blocking effects, that spell the difference between the atypical antipsychotics and the earlier drugs.

These properties seem to result in both lessened side effects and increased treatment effects—which means patients are more likely to stick with them. The new research found that while increased adherence accounted for a lot of the antiviolence effect, it was not the whole story. There did seem to be a genuine difference in the drugs' effects on the brain.

Consequently, the findings on the effect of the atypical drugs could support previous research that suggests a link between low serotonin levels and impulsive violence. Some studies have found, for example, that violent suicides are associated with low serotonin levels. Other research suggests that people who are violent toward themselves may also be prone to be violent toward others.

The atypical antipsychotic for which there is the strongest evidence of a reduction in violence, clozapine, also appears to be the best at reducing suicide, which is a serious risk with schizophrenia.

Meltzer says this research does not definitevely prove an association between low serotonin and violence. However, because the risk factors for suicide and violence toward others are similar, it would not be surprising if the same drugs reduced both, he says.

Swartz's research group also found that the atypical medications were significantly better at reducing substance misuse, a problem that affects roughly half of people with schizophrenia. Those who abuse alcohol and other drugs run the highest risk for becoming violent.

Because recreational drug use and violence dropped at the same time in the study, Swartz says it was difficult to tell whether the atypical medications were reducing violence by cutting drug craving or by some other mechanism. If these medications do curb cravings, they might provide insight for researchers looking to develop antiaddiction drugs. Meltzer says atypical antipsychotics would be "too toxic" for use in addiction without co-occurring schizophrenia because they can have significant metabolic side effects. Other drugs that affect the same receptors are being sought to fight addiction.

Alternatively, if the atypical antipsychotics reduce violent tendencies themselves, not just craving, understanding how they work might lead to development of antiaggression drugs with uses far beyond schizophrenia.

The cost of current medications is a significant barrier to wider use, however. A year's supply of the older medications is $500 or less; newer drugs run $6,000 to $10,000 or more annually, Swartz says. But cost/benefit analyses suggest that the new drugs are actually slightly less expensive or cost equivalent to society: By increasing adherence, they reduce the most expensive medical costs of schizophrenia—those of hospitalization due to relapse. If the new drugs reduce violence as well, cutting injury-related and criminal justice expenditures, the calculation would swing even further in their favor.

Maia Szalavitz is a freelance science writer from New York, N.Y.

RNAi: Running Interference on Disease-Causing Genes

BY BRENDA PATOINE

Of all the advances genomics research has spawned, few have caused such a stir among scientists as RNA interference.

A technique for silencing gene expression, RNAi, as it is called, has become an important tool for basic science investigations and has broad potential for treating neurological disorders, among others. It made *Science* magazine's prestigious Breakthrough of the Year list two years running and has set off a race among biotech companies to harness the technology for clinical use.

But a number of fundamental questions remain unanswered, leading some scientists to caution against rushing to test RNAi in humans.

"I think it's easy to get excited by this, and we should all be hopeful that RNAi can one day be applied to treat a wide range of disease," says Zuoshang Xu, a molecular neurobiologist at the University of Massachusetts Medical School who is developing RNAi-based therapies for amyotrophic lateral sclerosis (ALS). "But at the same time, I think we should take a step-by-step approach to clinical applications. We shouldn't be carried away by all this hype and jump too quickly."

Xu points to the pitfalls encountered in gene therapy research, when several patients either died or developed cancer in early clinical testing. These problems "seriously slowed the field because they created a huge negative perception in the public," he says.

Still, the potential for treating disease with RNAi cannot be ignored—and not just for dominantly inherited diseases but for virtually any disease involving abnormal accumulation of proteins, including Alzheimer's, Parkinson's, and Huntington's.

"There is definitely huge potential for enabling this technology" for human benefit, says Thomas Tuschl, a molecular biologist at Rockefeller University who has pioneered RNAi techniques. Although direct therapeutic applications have attracted the most attention, RNAi can also provide vital information about the molecular and genetic processes that lead to disease, which can then be used in developing traditional pharmaceutical compounds that might interfere with disease processes, he says.

A Wrench in Gene Activity

RNA molecules form the critical bridge between genes and the activity they generate in cells. Like their healthy counterparts, mutant genes, with the assistance of RNA, produce proteins, but the products of mutants set the disease process in motion. RNAi works like a well-targeted monkey wrench, "knocking down" the expression of disease-causing genes to prevent them from doing their dirty work.

In sporadic diseases not linked to a specific gene, RNAi may be used to block disease pathways to prevent or ameliorate symptoms. For example, in Alzheimer's disease, RNAi might be directed at "precursor" proteins and the enzymes that contribute to the buildup of the toxic protein beta-amyloid.

A recent report in *Nature Medicine* by Beverly Davidson and colleagues at the University of Iowa, in which RNAi was used to silence expression of the gene for the movement disorder spinocerebellar ataxia type 1 (SCA1), illustrates the technique's therapeutic potential in inherited disease. Mice treated with RNAi had improved motor coordination, and their brains no longer showed the cellular changes characteristic of the disease.

Despite promising reports such as Davidson's, there remains a lot of skepticism about how well RNAi will work in humans. Tuschl points out the Iowa team started the therapy early, before symptoms were apparent. Typically, he says, "by the time you diagnose someone with a degenerative disorder, it may already be at a point where you can no longer repair the damage."

Sparing Healthy Genes

A critical unanswered question is how to ensure that RNAi-based therapies target only the mutant genes and spare normal copies that may produce vital proteins. If RNAi mistakenly shuts down healthy genes, the results could be worse than the disease being treated.

Xu and others, notably Henry Paulson at the University of Iowa, have developed RNA constructs that seem to accomplish this precise targeting by exploiting mutations called single nucleotide polymorphisms (SNPs), which are naturally occurring differences in individual nucleic acid molecules, the fundamental building blocks of DNA. But the problem is far from solved.

"I think we got lucky," Xu concedes. "The mutations we tested were simply mutations that could be distinguished, but there are a whole bunch of others that are difficult to distinguish." In fact, he says, RNAi differentiates the majority of SNPs relatively poorly.

> ***"A critical unanswered question is how to ensure that RNAi-based therapies target only the mutant genes and spare normal copies that may produce vital proteins."***

Another huge hurdle, at least in brain diseases, is how to deliver therapeutic RNA molecules into the correct part of the brain. Scientists are pursuing two approaches, each of which has advantages and drawbacks. One strategy is to use a viral vector, as has been done with gene therapy. This has the benefit of regulating the targeted gene's expression for the long term, but it also raises the risk that the virus might be randomly integrated into the genome, which could cause cell death or activate tumor growth.

Others, including Tuschl, are testing synthetic versions of short RNA

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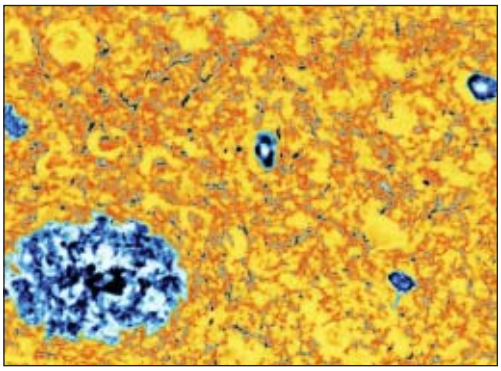
Alzheimer's Disease:
An Early Alert from the Immune System

BY SANDRA J. ACKERMAN



A plaque containing beta-amyloid, a marker of Alzheimer's disease, appears as a large blue area in this image of brain tissue. The disease has never been diagnosable with complete accuracy in living patients, but that may change thanks to clues from the immune system.

Since it was first described a century ago, Alzheimer's disease (AD) has been notoriously difficult to diagnose—in a live patient, that is. A suspected AD patient may show any or all of the common symptoms, such as trouble with language, memory, everyday decisions, or complex movements, but these lapses cannot be attributed solely to Alzheimer's disease.

Although most trained neurologists can now diagnose AD with about 90 percent accuracy, the only sure means of identifying it is by postmortem examination of the brain, which reveals the neuronal plaques and tangled nerve fibers that are the hallmarks of this disease.

Now, with the prospects for treating AD growing stronger by the day, the need for earlier diagnosis is becoming urgent.

"There are drugs already available that work best if started early" in the course of the disease, says Jerry Buccafusco, director of the Alzheimer's Research Center at the Medical College of Georgia and a co-author of a newly published study. Lead author Shyamala Mruthinti, instructor in pharmacology and toxicology at MCG, together with Buccafusco and their colleagues, think they have found a key to early diagnosis of AD in the careful measuring of certain immune responses.

The MCG scientists looked at immune reactions to two specific proteins, known by their abbreviated names, Aß1-42 and RAGE. These two play complementary roles in the formation of neuronal plaques, which in turn bring on inflammation and other toxic conditions in the brain. Mruthinti and her collaborators found that blood levels of the two proteins themselves were no higher in AD patients than in a control group. However, the immune *responses* showed a striking difference: The concentration of antibodies to Aß1-42 in patients with Alzheimer's was four times as high as in the control group, and the concentration of antibodies to RAGE was nearly three times as high.

To detect AD as early as possible, the MCG scientists would have to measure the antibodies before they had reached such a high level, most likely in people who had not yet begun to show any sign of the disease. This they are now attempting to do, along with colleagues at Georgetown and Duke universities

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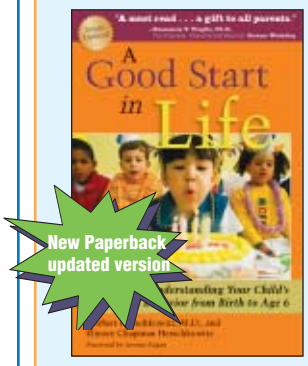

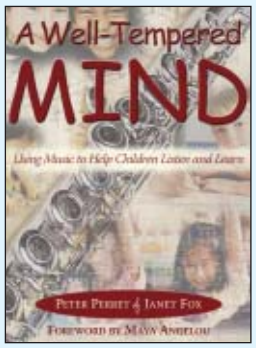

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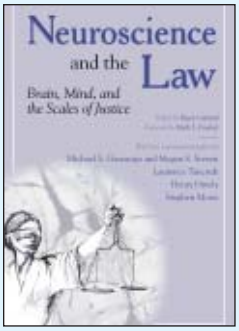

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News
FROM THE FRONTIER

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better recovery in general. The results represent a possible new approach to treating spinal cord injury, although such treatments would still require years of research and testing.

"Much of the focus of research has been on trying to regrow portions of the spinal cord," says Nedergaard. "We're trying to stop the damage up front."

••• **Substance abuse doesn't always act alone.** In a person who is receiving treatment for substance abuse or addiction, other psychiatric illnesses—for example, anxiety and mood disorders—often go untreated. Anxiousness, low mood, and other such symptoms have commonly been thought to arise from either intoxication with the substance or withdrawal from it. Now, however, a report from the National Institute on Alcohol Abuse and Alcoholism (NIAAA) shows that one in five Americans who are struggling with a substance disorder are also affected, independently, with a mood or anxiety disorder.

Published in the August *Archives of General Psychiatry,* the report draws on the largest-ever survey of "comorbidity," or co-occurrence, of substance abuse with depression, manic disorder, generalized anxiety disorder, panic disorder, or specific phobias. More than 43,000 adult Americans took part in 2001 and 2002 in interviews with trained employees of the U.S. Census Bureau.

The results make for grim reading. Within a 12-month time frame, 9.4 percent of those surveyed had a diagnosable substance-use disorder, according to the standard psychiatric reference manual known as *DSM-IV.* Of these 19 million people, about 3.7 million (more than 19 percent) were also diagnosed with a mood disorder, and about 3.3 million (more than 17 percent) with an anxiety disorder.

Ignoring these concurrent disorders is no longer an option, say the authors of the report. "Left untreated," they add, "mood disorders have been shown to lead to relapse of substance dependence and can also be fatal, as many former substance abusers with severe untreated independent depression will die by suicide."

Lead author Bridget Grant, chief of the NIAAA's Laboratory of Epidemiology and Biometry, cautions against reading too much into the strong correlations. "This study does not resolve questions about causal mechanisms that may underlie relationships between *DSM-IV* substance and mood and anxiety disorders," she says. A second round of surveys in 2004 and 2005 will gather more data, with the aim of shedding light on the cause-and-effect relationship between disorders of substance use and those of mood and anxiety.

••• **How learning can interfere with memory.** Young children are notoriously forgetful: They leave crayons in their pockets, shoes in the car, and a trail of sweaters and jackets wherever they go. Yet, according to a recently published study, they sometimes remember things more accurately than most adults. How do they manage to do so?

Vladimir Sloutsky, professor of cognitive science, and graduate student Anna Fisher suggest children think differently than adults: Whereas adults tend to sort objects into categories, children tend to compare similarities. For example, if told that a cat has "beta cells" in its body, adults will induce that another cat also has beta cells, because both creatures are cats. Children will come to the same conclusion, but their reasoning will be that the two creatures look alike.

Sloutsky and Fisher, both of Ohio State University, asked groups of 5-year-olds and college-aged adults to look at picture cards showing various cats, birds, and bears. In the next step the participants were shown some of the same cards, randomly mixed in with other cards not shown before, and asked which ones they recognized. As the authors relate in the August issue of *Psychological Science,* children outperformed adults on this task, easily distinguishing between new pictures and ones they had seen earlier.

The children were then taught to reason in an adult manner and given practice tasks to help them get used to this mode of induction. When they tried their hand again at picture-card recognition, they performed more poorly than before—in fact, their scores fell as low as those of the adults.

These results reveal a new aspect of learning: Although abstract mental categories allow us to take in enormous amounts of new information, they make it all too easy to overlook specific details. "It's one case where knowledge can actually decrease memory accuracy," Sloutsky says.

••• **Lighting up: Like mother, like teenager?** Adolescents whose mothers smoked during pregnancy are more likely to take up smoking themselves, and to become addicted to nicotine, than their nonexposed peers. The effect of prenatal nicotine exposure appears strong even in studies that account for psychological factors such as childhood environment and adolescent peer pressure. What could be the physiological basis for it?

A research team led by pharmacologist Theodore Slotkin of Duke University set out to answer this question. As they report in the August issue of *Neuropsychopharmacology,* the scientists gave either nicotine or a placebo to female rats throughout their pregnancy, and then again to their offspring during a brief period of adolescence, roughly 30 to 48 days after birth.

Slotkin and his colleagues found that exposure to nicotine before birth reduced the number, size, and functional surface area of neurons in the brains of gestating pups. When those offspring were exposed to nicotine during adolescence, they showed greater neuronal damage and addictive potential than did their previously unexposed peers. Thus, exposure to nicotine in utero makes the brain more vulnerable to damage from "smoking" at a later stage of development.

The next step, for this research team, is to explore other correlations that have been observed between maternal smoking and disorders in offspring's brains and bodies. Says Slotkin, "We're now studying the relationships between prenatal nicotine exposure and subsequent disorders such as depression and obesity."

—S.J.A

(RNAi, continued from page 5)

stretches—small molecules that would also need to be injected into the brain or infused via catheters or biodegradable pumps, but which induce only a transient silencing of the target gene. This means patients would need repeated treatments, possibly every couple of weeks. On the upside, "synthetic RNA has the advantage that you can just stop the treatment" if need be, says Tuschl. Moreover, he notes, "you don't have the cancer problem to deal with."

At least two biotech companies are hoping to start clinical trials this year in ocular diseases, considered a "low-hanging fruit" for RNAi because the molecules can be injected directly into the eye. In addition to neurological diseases, RNAi is being investigated as a treatment for diabetes, obesity, HIV, and hepatitis.

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

(ALZHEIMER'S, continued from page 6)

and the University of Vermont, in a collaborative project sponsored by the National Institutes of Health. The study focuses on people with a condition known as mild cognitive impairment, which carries with it a somewhat higher risk—but by no means a certainty—of AD.

The purpose of the project is to evaluate nicotine patches (now used mainly as an aid in stopping smoking) as a possible treatment for mild cognitive impairment. But the results from Mruthinti's study have been so striking, says behavioral pharmacologist Ed Levin, a collaborator at Duke, that "we are including the antibody measurement in the NIH study as well."

Levin adds, "I think the study from MCG will have a real impact in our field, in two ways. First, highlighting the role of the anti-Aß1-42 and anti-RAGE antibodies may be important in helping us understand how Alzheimer's disease begins. And second, this work may point toward a new way of predicting who is likely to develop AD. It's true that we can now treat the disease once it appears, but I think everyone agrees that preventing it from developing would be even better."

Sandra J. Ackerman writes about science and medicine from Durham, N.C.

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