THE DANA FOUNDATION'S

BRAINWORK

The Neuroscience Newsletter

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News FROM THE FRONTIER

••• **An Autism Risk Gene?** The causes of autism remain a great mystery, though researchers have come to agree that genes play a major role in susceptibility to the disorder. Genetic clues have been slow in forthcoming, but a study published in the April issue of the *American Journal of Psychiatry* has yielded a promising candidate.

Unlike previous studies, which identified rare mutations associated with autism in single families, the current one by Joseph Buxbaum and his colleagues at Mount Sinai School of Medicine in New York City focused on risk genes in 411 families with a history of autistic spectrum disorders. They found that slight changes in a particular gene doubled the likelihood of having autism.

A bonus finding is that this gene is already known to biologists. The protein it codes for plays a role in producing energy for cells. There are some hints, but no firm evidence, on what role the cellular energy machinery might play in causing autism.

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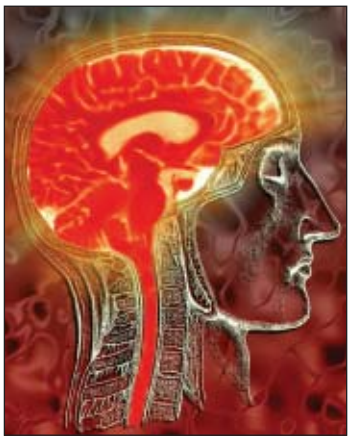
Inflammation in the Brain:

When Good Molecules Go Bad

BY BRENDA PATOINE

Inflammation is one of the body's basic mechanisms for "host defense," serving an integral role in the immune response against pathogens and in tissue recovery following injury. Yet, in the brain and central nervous system (CNS), the inflammatory response can quickly spiral out of control, causing secondary damage to neural tissue that can exacerbate an injury or chronic disease condition.



Understanding inflammation could lead to new therapeutic methods for neurological problems.

This "inflammatory cascade" is now recognized as a significant contributor to brain damage following acute CNS injuries such as stroke and head or spinal cord trauma, and in recent years its role in chronic degenerative diseases such as Alzheimer's and Parkinson's has become increasingly clear. As scientists delve into the underlying mechanisms that can turn a normal physiological response into a destructive pathogenic process, new targets are emerging that may be viable for therapeutic intervention. The challenge, say experts, is figuring out how to home in on the bad effects of inflammation while sparing those aspects that serve useful roles.

"People who study neurological insult, whether of the acute or chronic kind, are by now very thoroughly convinced that inflammation is not only a bad thing, but that secondary inflammatory damage in the nervous system accounts for a significant percentage of the neurons lost," says Robert Sapolsky, a neurobiologist at Stanford University's Brain Research Institute. "Within this framework, there is definitely still the recognition that a moderate or 'reasonable' amount of inflammation is in some ways protective."

The problem, Sapolsky adds, is that "the brain is pretty lousy at making sure that moderate inflammation doesn't spiral out of control."

Unique Immune Status

By all accounts, the brain is unique in its response to inflammatory processes set in motion by immune-system activation. For one thing, it is encased in the hard shell of the skull, which constrains swelling. In addition, the blood-brain barrier seems to protect the brain from the normal traffick-

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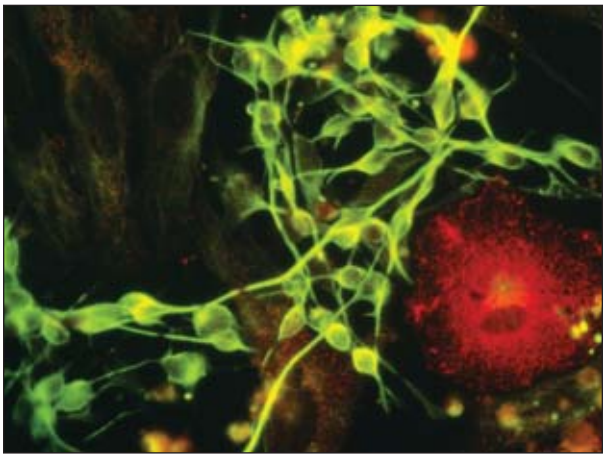
(INFLAMMATION, continued from page 1)

ing of immune cells called lymphocytes that occurs in other body systems, though there is increasing evidence that some of these cells do find their way into the CNS.

The brain also has its own exclusive brand of innate immune cells, microglia, which are not found elsewhere in the body. Cousins to macrophages, the scavenger cells that patrol the body and gobble up offending pathogens or foreign cells, microglia are the brain's waste-management staff: they are dispatched, for example, to clean up the residue when neuronal cells die. Yet as the resident CNS immune sentinels, they don't seem to rev up the immune response the way macrophages outside of the CNS do, even when directly infected with a pathogen.

Experts say there are good reasons for this: As immunologist Joan Goverman of the University of Washington, Seattle, puts it, "The brain is not the place where you want to start a war." Michael Dustin, an immunologist at the New York University School of Medicine, suggests that microglia may "set up an environment in the CNS in which some level of immunological responsiveness is sacrificed in order to preserve the brain system" of synaptic connections, which store memories and underlie critical cognitive functions.



Microglial cells such as this one, stained red, help keep the brain free of foreign invaders. Inappropriate or extended activation of such cells can lead to a cycle of damage-causing inflammation.

Still, the actions of microglia and of the more widespread macrophages have similarities. When activated, they express many of the same proteins normally associated with inflammation, such as cytokines, chemokines, and complement proteins, as well as glutamate and other brain chemicals that can be toxic to neurons. At appropriate levels, these substances serve useful roles, such as combating infection or stimulating general defense responses such as fever and overall lethargy, which can facilitate recovery.

Separating Good from Bad

"Physiologically, microglia are there for a reason. They do good," says Daniel Laskowitz, a clinical neurologist at Duke University Medical Center. The trouble starts when microglia are either inappropriately activated, as in stroke, or are activated too robustly or for too long, which may occur in neurodegenerative diseases. This sets off a rush of neurotoxins that promote secondary inflammation while at the same time causing more microglial activation. "The whole thing is like a giant feed-forward loop," he says.

The cytokines and other pro-inflammatory proteins released in this cascade "are not always bad molecules," says Nancy Rothwell, a biologist at the University of Manchester, U.K. "There are lots of examples in biology of molecules that, when they're doing their job right, they're fine." She says the "overactivation" response is not unlike what happens in conditions like rheumatoid arthritis, when the immune system overreacts, or to stress-related diseases, which are marked by overproduction of stress hormones.

Stress hormones, it turns out, are somewhat of a wild card in the inflammatory cascade. Scientists have begun to take a new view of these potent hormones, a family known as glucocorticoids, long considered to be exclusively anti-inflammatory in their actions. While no one questions that glucocorticoids have powerful anti-inflammatory effects outside the nervous system, recent data, typified by work from Sapolsky's laboratory, have led to "the recognition that they are often only weakly anti-inflammatory in the injured brain, and in fact can have utterly unanticipated pro-inflammatory effects," says Sapolsky.

This emerging view of stress hormones "strikes us as hugely important," Sapolsky says, and not only at the "gee-whiz level" of challenging longstanding dogma: "There is this complete mystery of how this hormone seems to have absolutely opposite effects on similar cell types, depending on where they are in the body and, perhaps, on what the circumstances are." His group recently reported, with surprise, that glucocorticoids caused an increase in relative numbers of inflammatory cells and in levels of pro-inflammatory cytokines when administered to rats following neurological trauma. Such new under-

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Editor
Dan Gordon

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Design
FTM Design Studio

A PUBLICATION OF THE DANA PRESS

Jane Nevins, Editor in Chief
Walter Donway, Director

Editorial office:
The Dana Center
900 15th Street, NW
Washington, D.C. 20005
E-mail: danainfo@dana.org

THE DANA FOUNDATION
745 Fifth Avenue Suite 900
New York, NY 10151

For free subscription or change of address:
rtalley@dana.org, or fax to 202-408-5599

BrainWork on the Internet: www.dana.org

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standings "sure bring into question the massive use of glucocorticoids as anti-inflammatory compounds in the realm of neurology—something the best people have been questioning for years," Sapolsky says.

Seeking New Approaches

Doctors see an urgent need for new approaches to quell secondary inflammation, both in acute injury and chronic disease. "There's a cascade of brain inflammation that probably peaks in the first three or four days that we're not targeting at all," says Laskowitz, who treats patients with stroke or head injury in Duke's neurointensive care unit. "We kind of sit back and wait until brain swelling becomes life-threatening, then take reactive measures—none of which have ever been shown to improve functional outcomes."

The brain "probably has a very limited repertoire of responses to a variety of very diverse diseases."

It turns out that the brain "probably has a very limited repertoire of responses to a variety of very diverse diseases," he says. "If you could harness that inflammatory response as a therapeutic target, in theory, it would be relevant to chronic neurodegenerative disease like Alzheimer's and classic neuro-inflammatory diseases like MS (multiple sclerosis) or HIV encephalitis, as well as more acute conditions like stroke or traumatic brain injury."

Laskowitz believes it's likely that microglia, with their complex intracellular machinery, have more than one pathway toward activation, and therein may lie the key to taming overactivation. "The question is, can you differentiate the pathway that causes secondary neuronal injury from the pathway that may be involved in protective and adaptive responses?" he asks.

In searching for an answer, Laskowitz focused on apolipoprotein E (apoE), a protein best known for roles in cholesterol transport and Alzheimer's risk. In a series of experiments, his team showed that apoE inhibits microglial activation and seems to inherently change how the brain responds to injury. He and other groups have shown that one variant of the gene that encodes apoE, the e4 allele, worsens a number of neurological conditions in addition to Alzheimer's, including multiple sclerosis, traumatic brain injury, intracranial hemorrhage, and neurocognitive deficits following cardiopulmonary bypass surgery.

Laskowitz's team is now concentrating on developing therapies based on apoE, including a small molecule that mimics the receptor-binding region of the protein. Recently published data showed that, when given intravenously to mice, the so-called apoE mimetic reduced inflammation and improved outcome following a closed head injury. While his initial preclinical studies have focused on head injury, Laskowitz believes that "modifying that pathway as a therapeutic strategy is probably relevant for more than one disease."

Another possible therapeutic approach to modifying post-injury neurological damage that seems promising based on early preclinical data is being pursued by Rothwell's group. Their strategy centers on manipulating the expression of interleukin 1 (IL-1), a key inflammatory cytokine that is released by microglia. Her team has recently completed a small safety study in stroke patients using a naturally occurring molecule that blocks the IL-1 receptor. The hope is that, by inhibiting the action of IL-1, secondary damage from post-stroke inflammatory processes will be limited.

Rothwell is "cautiously optimistic" that this approach may one day be a viable treatment option for acute stroke, and possibly for other CNS injuries such as head trauma and subarachnoid hemorrhage, since the underlying mechanisms are very similar.

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

Antidepressants for Children:
Is There a Safe Choice?

BY SANDRA J. ACKERMAN

From the point of view of a clinician, depression presents a paradox. Although in adults it is one of the mental illnesses most amenable to treatment, depression in children and adolescents is notoriously difficult to treat.

To make matters worse, a common medical intervention has now become highly controversial, with several new studies suggesting an association between young people's use of these medications and an increased risk of suicide. Is drug treatment for children with depression actually dangerous—perhaps even more dangerous than depression itself?

"The real dilemma has been that we've not had a lot of good medication for depression in children," says Richard Walls, a member of the Committee on Drugs of the American Academy of Pediatrics.

Several different families of drugs, most recently the SSRIs (selective serotonin re-uptake inhibitors), have proved effective for adults, lightening the burden of depression for more than 80 percent of all those treated. In addition, several million children in this country take some form of SSRI for depression, according to David Fassler, a practicing child-and-adolescent psychiatrist. However, only one of the SSRIs, fluoxetine (sold under the brand name Prozac), has received approval from the Food and Drug Administration specifically for treating depression in children and adolescents.

The reports that are raising red flags include both published and unpublished studies and anecdotal evidence, and they come from abroad as well as from the United States. In Britain, in what some American researchers consider an overreaction, the government's drug regulatory agency has banned the prescription of all SSRIs,

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(ANTIDEPRESSANTS, continued from page 3)

except Prozac, for children.

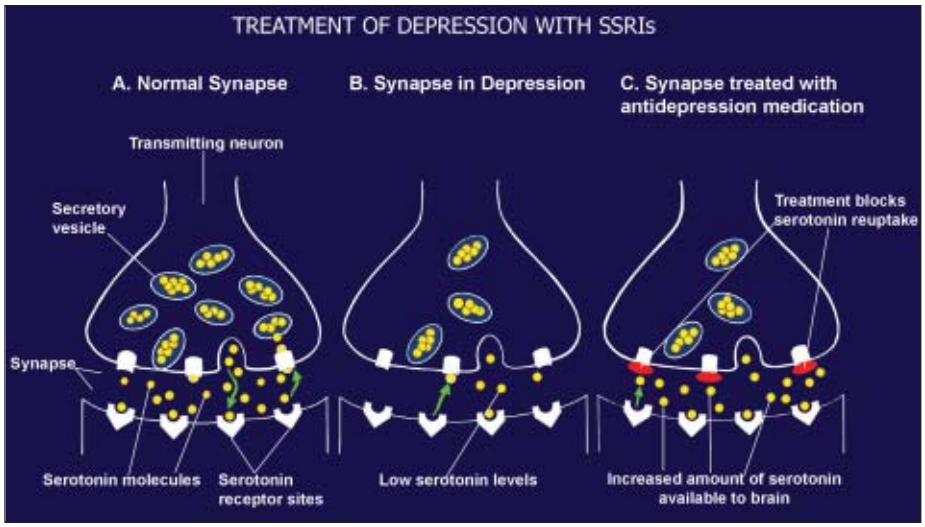
In this country, the FDA held a public hearing on the topic in February and in March issued a Public Health Advisory, urging clinicians, patients, and the families of patients receiving SSRIs to be alert for any increase in depressive symptoms such as anxiety, insomnia, or impulsivity, and for the possible emergence or worsening of suicidal thoughts or actions.

The FDA has asked the manufacturers of ten leading antidepressants to change the wording of their warning labels to reinforce the need for close monitoring of both children and adults with depression, particularly in the first few weeks of treatment. Meanwhile, the reports that fueled this controversy are undergoing an independent review from researchers at Columbia University, who are expected to state their findings sometime this summer.

To put these alarming developments in perspective, it is important to remember that depression itself greatly increases a person's risk of suicide; indeed, postmortem studies of adolescent suicide victims have revealed traces of underlying depression in the great majority of them. Do antidepressant drugs increase this risk even further?

"No, they do not," says Joseph Coyle, professor of psychiatry and neuroscience at Harvard Medical School. Coyle says most adolescents in the post-mortem studies likely had received no treatment at all for their depression; even in those who had committed suicide while apparently under treatment, the levels of antidepressant medicine found in their systems were extremely low.

A recent study headed by researchers at the New York State Psychiatric Institute shows that, far from contributing to the risk of suicide, the use of SSRIs appears to lower it. Among people age 15 to 19, every 1 percent increase in the use of these antidepressants corresponds to a drop in suicide rates of 0.23 per 100,000—which adds up to two or three young lives saved every year. This inverse correlation does not prove that the use of SSRIs for depression directly lowers the risk of suicide, but it clearly argues against the likelihood that these medications add to the risk.



Selective serotonin re-uptake inhibitors, or SSRIs, treat depression by making more serotonin available to the brain. Their use in children, however, is under intense scrutiny because of concerns about suicide risk.

"Since a lot of new data came out at the FDA hearing, it's now harder to make a definitive statement" about the use of SSRIs for young people, says Dennis Charney of the National Institute of Mental Health. "If I were faced today with a child with depression, I would still use an SSRI," he adds. "But I would monitor the child carefully, and obviously the parents would have to do the same." In addition, according to pediatrician Richard Walls, treatment with an SSRI should always include some type of psychotherapy.

"At the hearing in February the FDA took a close look at the various studies to try and detect any potential link with an increased risk of suicide," says Fassler, who testified there on behalf of the American Psychiatric Association. "Some studies seemed to show a slight increase in the rate of

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RESEARCH NEEDED ON YOUNG PEOPLE

To make the most effective use of the depression treatments now available will require clinical trials designed specifically with children and adolescents in mind. The safest and most efficacious dosages, the incidence and types of side effects, all must be determined anew for people from about age 5 to 10 and, separately, from 11 to 19.

"A child is an evolving, developing, growing being; you can't assume that what works for an adult will work the same way for a child," says Richard Walls, a member of the Committee on Drugs of the American Academy of Pediatrics.

The Pediatric Research Equity Act, enacted by the U.S. Congress in 2003, calls upon drug companies to conduct pediatric studies of any new medications and adds, as an incentive, an extra six months of market exclusivity. Such studies are now in the planning stages.

Studies focusing on children face a few extra challenges; for example, obtaining informed consent from 10-year-olds and their parents calls for a different approach from the standard procedure used with adult subjects. Also, Walls says, "Many parents shy away from enrolling their children in a study, not realizing that the safest place for a child to be is in a study, where he or she will be very closely monitored and promptly treated for any problems that arise."

Recruiting large numbers of subjects is a crucial goal for the next round of studies. Says David Fassler, a practicing child-and-adolescent psychiatrist, "If you add together all the patients from all the studies reviewed for the FDA hearing, you have only about 4,000 kids, which is still a relatively small sample, given all the variables involved. We clearly need additional studies to help us answer the key questions about both safety and efficacy."

—S.J.A.

Clogged Cells Contribute to Neurodegeneration

BY RABIYA S. TUMA

Just as cities rely on recycling and sanitation programs to keep streets clear of garbage, cells have a highly regulated system for breaking down and recycling damaged or unwanted proteins. Now, researchers are finding that disruption of the cell's cleanup system contributes to the pathology of neurodegenerative diseases—and can lead to neuronal cell death.

The structure responsible for removing unwanted proteins is called the proteasome. When everything is running as it should, unneeded, damaged, or improperly folded proteins are tagged with a small flag called a ubiquitin molecule. As soon as a protein is bound by four ubiquitins, it is transported rapidly to the proteasome. Once there, the proteasome chews up the protein into individual amino acid subunits, which can be used in the synthesis of new proteins.

Protein Problems

The degradation process is rapid once it starts, so researchers find few ubiquitin-tagged proteins in healthy cells, says Ron R. Kopito of Stanford University. However, one of the hallmarks of many neurodegenerative diseases is misfolded proteins—such as the beta-amyloid proteins that make up the plaques in Alzheimer's disease—and some of these are tagged with ubiquitin. Thus, something appears to be going awry with the cell's cleanup system in these disorders.

To find out what the problem is, Kopito and other researchers have been studying the normal function and biogenesis of the proteasome, as well as its behavior in the presence of proteins associated with neurodegenerative disorders. Although it is not yet clear exactly where the problem starts, scientists are sure that malfunctions in the proteasome system are involved in the diseases and that such problems can lead to neuronal death.

To find out if this sort of backup of the disposal system is typical of neurodegenerative disorders, Kopito's team looked at what happens to proteasome function when cells express the form of Huntington's protein that is associated with the disease. In healthy individuals, the Huntington's protein contains a stretch of approximately 25 glutamine amino acids in a row. In people genetically predisposed to the disease, that run of glutamines can stretch to more than 100. These large stretches of glutamines stick to one another, forming unwieldy globs of protein.

To learn how such aberrant proteins affect proteasome function, the scientists engineered a protein that was fluorescent and contained either 25 or 103 glutamine residues, as well as a signal that tells the cell to tag it with ubiquitin. In neurons expressing the shorter protein, little fluorescence accumulated, indicating that the proteasome system was working efficiently enough to prevent a buildup of the engineered protein. However, neurons expressing the protein with 103 glutamines glowed brightly. That means the presence of these sticky, long stretches of glutamines inhibits proteasome function in some way, Kopito says.

The team found similar results with ataxia 1, a protein associated with spinocerebellar ataxia type I, a neurodegenerative disease that causes movement disorders, vision problems and muscle weakness. These comparable results in multiple disorders suggest that disruption of proteasome function may be a common malfunction in neurodegenerative diseases.

Kopito proposes two explanations for these results: Either the overwhelming amount of misfolded protein is physically clogging the proteasome, which would be akin to someone stuffing so much detritus into a garbage disposal that it can't function, or some stimulatory signal that tells the proteasome to become active is sequestered by the enormous amount of aberrant protein. Although it is not yet clear which mechanism occurs, Kopito's work strongly suggests that the presence of such misfolded protein clumps inhibit normal proteasome function.

Dynamic Structure

Jeffery Keller's group at the University of Kentucky is taking a different approach to studying proteasomes and their role in neurodegenerative diseases. Before they challenge cells with unhealthy situations, they are working to learn how the system behaves under normal conditions.

Although the proteasome functions like a typical enzyme, using energy to change one thing (the unwanted protein) into something else (single amino acids), it is much more complex than most enzymes. It is a large structure with multiple subunits, the largest of which is made up of 28 proteins. Not all cells use the same 28 proteins to build that subunit, and, furthermore, cells can change both the composition and amount of different proteins they do make. Thus, what many researchers saw as a static functional unit is, in fact, a highly regulated and changeable structure, one that appears to alter its components based on the needs of the cell.

For example, when cells are stressed by the presence of reactive forms of oxygen, which attack proteins, the cells react by increasing the amount of proteasome subunits they produce. This change augments the number of functional proteasomes in the cell and enables it to clean up all the compromised proteins. However, when Keller's group exposes cells to these oxygen radicals and simultaneously blocks the upregulation of the proteasome, the cells can only tolerate it for a couple of hours, then die off.

Unlike Kopito's team, Keller's group finds that proteasomes work fine in the presence of protein aggregates, although cells in the mouse models of Huntington's disease express lower levels of proteasome proteins and seem to have less ability to respond to subsequent stresses. For example, if the researchers expose cells containing protein aggregates to reactive oxygen

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When the Brain Calculates Language

If you read this sentence out loud or someone reads it to you, you will be able to distinguish each word from its neighbors—and, likely, it will sound as if there are spaces residing between the words, apparent voids of sound that break spoken language into the functional word units.

In fact, pictures of amplitude over time show that there are no real spaces between words and that quiet or low volume spots in a sentence are part of the sounds. That leaves linguists with a puzzle: How do language learners distinguish where one word starts and another stops?

It turns out that as people hear a language over time they naturally—and passively—record the likelihood that one sound will appear next to another, says Elissa Newport of the University of Rochester in New York, who presented her work at the American Association for the Advancement of Science conference in Seattle in February. Take, for example, the run-together "prettybaby." Over time, an English language learner recognizes that while the sound "tty" often follows "pre," it rarely precedes "ba." Therefore, we know the word break occurs between "pretty" and "baby."

To demonstrate that our brains really do perform such statistical analysis of the language around us, Newport brought volunteers into a room and asked them to try to decipher the six words of a made-up language after listening to a computer voice randomly repeating the words. When she asked them later to pick out the words from groups of sounds that resembled the made-up words, they were able to distinguish all six.

In recent work, Newport has explored this concept more fully and has found that children use similar statistical analyses when learning a language from their parents. Scientists already recognize that children often are more fluent in a language than their parents, even when mom and dad are their primary teachers. To understand how this comes about, Newport studied deaf children born to hearing parents who learned sign language as adults. As with spoken language, Newport finds that even though the parents are the ones teaching their children sign language, the children become more proficient users. In Newport's sample, the parents signed accurately between 20 and 75 percent of the time. The children were accurate with 80 to 90 percent of their signs.

"Humans are adept pattern learners." Even when there are errors the pattern can be deciphered—as long as the errors are inconsistent.

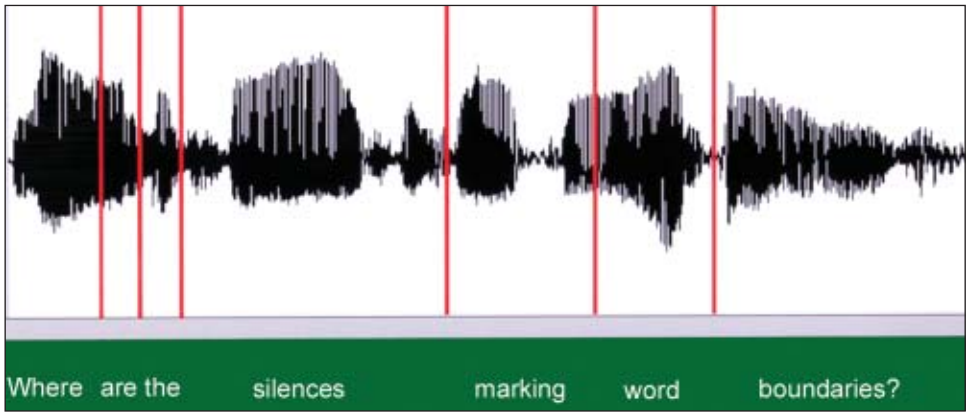
The key to this improvement by the children is that when the parents make mistakes they make all kinds of mistakes, not the same one over and over. Based on language experiments in the laboratory, Newport finds that this scatter is critical.

Again, she and her colleagues created a mini-language—complete with verbs, nouns, prepositions and rudimentary grammar—and tested adults and children in their ability to learn it. They found that if the computer "parent" got it right or made one type of error consistently, the language learner had trouble deciphering the correct pattern. If, however, the computer got it right some of the time but made a variety of inconsistent errors, the learners nearly always learned the correct pattern and regularized it in their own use.

Newport concludes that "humans are adept pattern learners" and that even when there are errors the pattern can be deciphered—as long as the errors are inconsistent.

Judy Shepard-Kegl, Director of the Signed Language Research Laboratory and Professor of Linguistics at the University of Southern Maine in Portland, concurs that children perform statistical analysis on the input around them. Working with deaf children in Nicaragua, she sees the children copy what their parents do. But, she says, they also see what others do. With all this input, the learners try to generalize what they hear, allowing them to pick out the most consistent or useable forms of the language around them.

—Rabiya S. Tuma



A waveform, such as the one shown here, is a picture of the loudness of a speaker's voice over time and shows that there are no sound breaks between words.

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Buxbaum stresses that the results need to be replicated in additional groups of subjects. But he and his colleagues are already examining the function of the gene in cellular and animal systems. "We can thereby determine the effects of over- or underexpression of the gene on cellular function and animal behavior," Buxbaum says.

••• **Infectious Prions It Is!** For his heretical notion that there could be infectious diseases not caused by bacteria or viruses—and their genetic codes of DNA and RNA—Stanley Prusiner eventually won the Nobel prize, in 1997. Yet clear evidence has never been produced that abnormal prion proteins could alter normal proteins, causing infectious diseases such as "mad cow" and related neurological disorders.

Two articles published in the March 18 issue of *Nature*, by independent groups of researchers, appear to have provided the coup-de-grace for the prion hypothesis.

Chih-Yen King and Ruben Diaz-Avalos of Florida State University and Jonathan Weissmann and colleagues at the University of California, San Francisco, developed separate experimental systems devoid of DNA or RNA. Under these conditions they induced abnormal yeast prion proteins to alter normal proteins. What is more, they produced prions with different shapes, or conformations, a previously troublesome challenge to the prion hypothesis. Some researchers had argued that such variations necessitated some sort of genetic material.

In an editorial in the same issue of *Nature,* Mick F. Tuite of the University of Kent in England writes that the papers "provide the most dramatic demonstration to date of the validity of the protein-only hypothesis." According to Tuite, researchers can now turn their full attention to the questions of how the abnormal forms of the protein are produced, maintained, and propagated to other proteins.

••• **Blocking the trauma.** One of the clever features that has evolved in the brain is the ability to file away information from a single event in different ways. A study published in the March issue of the *Journal of Experimental Psychology* suggests that understanding how these filing systems work could help people interfere with the storage, and unwelcome recall, of especially traumatic events, a major feature of post-traumatic stress disorder (PTSD).

Scientists showed videos of horrific accident scenes to study subjects, who were asked to perform minor distracting tasks during the viewing. Psychologist Emily Holmes and her colleagues at University College of London found that tapping keys repetitively on a keyboard significantly reduced memories of the accident scenes in the following week. By contrast, performing a verbal task involving counting during the video had the opposite effect—subjects were bothered by more memories.

The key to these differential effects appears to be parallel memory systems. As one system encodes simple visual images of an event, a higher-level system creates a more complicated narrative memory that helps the brain make sense of the event. Holmes and her colleagues suggest that the typing task competed with the simpler system, meaning that fewer potentially intrusive images were encoded. The more complicated verbal task, on the other hand, interfered primarily with the formation of complex memories that the brain might use to get perspective on the traumatic events.

Although the research is at an early stage, it may prove therapeutic for people at risk of PTSD. "It would be very helpful to examine these tasks immediately post-trauma, such as in the emergency room," Holmes says.

••• **One's brain, another's pain.** When you empathize with a friend who has just hit her thumb with a hammer, is this empathy neurologically equivalent to the emotion you feel when you hit your own thumb? The answer appears to be yes, according a study in the Feb. 20 issue of the journal *Science*. Tania Singer and her colleagues at University College of London show that some of the same brain regions activated when we experience pain also light up when a loved one is exposed to a painful stimulus.

Scientists have theorized that in order for social creatures such as humans to respond effectively to the pain of those around them, the brain should experience that pain in much the same way as pain to the "self," but lacking the sensory aspect. Singer and her colleagues devised a brain imaging experiment to determine whether any areas of the brain's "pain matrix" are involved in an empathic response.

As MRI machines scanned their brains, female subjects were exposed to mildly painful shocks. The subjects could also tell by indicator lights when their romantic partners were receiving shocks, but could not see their partners' faces. This eliminated the potential confound of an empathic response to facial expressions of distress.

"Self" pain activated the entire pain matrix, including areas involved in the sensation and discrimination of the painful stimulus, as well as areas that code for the subjective emotional (affective) response to pain. "Partner" pain also activated part of the pain matrix, but only areas associated with the affective component of pain.

"These brain areas allow us to understand and predict emotions in ourselves, as well as to understand and predict emotions in others," Singer says.

A feature story on empathy appeared in the July-August 2003* BrainWork, *available via www.dana.org.

"News" is written by Hakon Heimer, a science and medical writer in Providence, R.I.

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molecules, the cells are unable to upregulate their proteasome production and eventually die.

These observations are critical, says Keller, because as people age the proteasome activity in their cells drops off—and age is a major risk factor for all neurodegenerative diseases. Thus, when cells in older individuals are exposed to oxygen radicals, which are a normal byproduct of cellular metabolism, their cells are taxed but okay. If, however, their neurons also begin to accumulate aberrant proteins, like those associated with Alzheimer's, Huntington's, or Parkinson's disease, the combination is too much for the cells, and they will likely die.

"I think in any neurodegenerative condition associated with aging, oxidative stress [reactive forms of oxygen], or protein aggregates, we are going to find that the proteasome is clearly playing a role," Keller says.

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

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suicidal thinking or behavior with the medication, while other studies seemed to show a slight decrease."

One thing that became clear was considerable inconsistency in the gathering of data; for example, each study set its own guidelines for what constituted "suicidal" thinking or behavior. On a brighter note, Fassler points out, "In all the studies that were reviewed, there was not one actual suicide."

Coyle, who trained in pediatrics before becoming a psychiatrist, says, "It strikes me that cancer is No. 4 or 5 in causes of death for children, and the treatments we use for cancer have terrible side effects—they can even kill. Yet few parents would refuse surgery, radiation, chemotherapy, or any other treatment for their child if they thought it would help him beat cancer."

Like some forms of cancer, depression that is left untreated can lead to long-term disability or even death; in fact, suicide is the third most common cause of death among adolescents today. The parents of children with depression, therefore, must weigh the still unclear risks of SSRI treatment against the very real risks of allowing the depression to run its course.

Although the safety of SSRIs for children and adolescents requires further study, a great many clinicians and researchers continue to regard their use as a prudent choice. As Fassler puts it, "In many, if not most, cases, the benefits outweigh the risks."

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

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