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PROGRESS REPORT ON BRAIN RESEARCH

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by Mahlon R. DeLong, M.D., and Thomas Wichmann, M.D.

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INTRODUCTION

by Eve Marder, Ph.D.

President, Society for Neuroscience

I bring here perspectives of an unabashed and unapologetic basic scientist looking at a Progress Report that summarizes recent findings of fundamental importance to us and our families as we live our present lives and face our futures.

As a scientist, I have been privileged to work on the most basic of neuroscience problems, such as homeostatic regulation (maintaining stable neuronal function over a lifetime), only to discover that scientists interested in clinical problems such as epilepsy find it relevant to their work.[1, 2] At the same time, as a daughter, I watched with amazement as my father recovered from traumatic brain injury suffered as a consequence of a traffic accident. To this day I marvel at the extent to which his then 76-year-old brain rebuilt itself so that, almost seven years later, no one meeting him for the first time would dream that anything untoward had happened.

That said, his recovery is more a testament to the extraordinary ability of the human brain to recover from insult, and to the skill of a surgeon, than it is to our understanding of how and why his recovery was so complete. There is nothing more disconcerting to a neuroscientist than watching a close friend or family member dealing with a brain injury or disease, knowing how little we presently understand, and I welcome all of the advances described in this volume.

As a research scientist working in a liberal arts university, I teach a course titled "Principles of Neuroscience" in which I cover the full range of basic neuroscience and its application to issues of direct clinical and human problems. As an educator, I find extremely satisfying the astonishing numbers of instances in which arcane details addressed by scientists following the most basic of research topics set the stage for understanding clinical conditions. Likewise, in this collection of essays, I find equally satisfying the numerous instances in which work done over many years by basic scientists

has led to important advances that will eventually result in enhanced human outcomes.

One of the great mysteries of our lives is why and how individuals, growing up in families of all kinds, become painters, musicians, or dancers. We all have noticed the degree to which aptitude and practice of the arts "runs in families." Is that due to genetics, to early exposure and training, or to both? There are urban legends that mathematicians and physicists make good musicians. Is there really a connection with the cortical states that allow individuals to do formal abstract thinking and music? Will educating our children in the arts enhance other kinds of cognitive development? These are the kinds of questions that the Dana Arts and Cognition Consortium has begun to address.

Disorders that affect children, such as autism, attention-deficit/hyperactivity disorder, and mental retardation, are among the most heartbreaking of all neurological problems. Also devastating are neurodegenerative diseases, such as Huntington's disease, Parkinson's disease, and Alzheimer's disease, that affect adults. Recent work shows the power of genetics in understanding the causes of some of these disorders. Indeed, we are seeing today the fruit of decades of work on fundamental genetic mechanisms, as we now have the tools to study the role of interactions of multiple genes in complex human disease. The same message emerges from recent work on brain tumors: Much hope for developing new treatments for gliomas and other brain tumors is coming from studies of the cellular signaling pathways that are controlling the growth and proliferation of cancers of all kinds, including those of the brain.

It was rapid surgical intervention that saved my father's brain, and recent progress on stroke, highlighted in this volume, shows that timely intervention is also crucial for the protection of the brain in response to stroke and transient ischemic attacks that produce seemingly minor neurological effects. Timely interventions following a transient ischemic attack are now shown to decrease the risk of an additional, more serious, stroke in the weeks following the first evidence of ischemic neurological events.

In many human disorders it can be particularly difficult to translate the intuitions and findings from animal models into clinical practice. Excellent and well-controlled clinical trials are critical for this enterprise, but it can often be difficult to ensure that clinical trials are done correctly. Toward this end, the International Campaign for

Cures of Spinal Cord Paralysis has worked to develop new criteria for patient participation and assessment in clinical trials of potential treatments for spinal cord injury. Equally important are the criteria for clinical trials in all arenas in which evaluation of treatments for any neurological or psychiatric disorder is needed.

The past year has seen a remarkable explosion of interest in a series of issues, grouped together in the young field of neuroethics, to which the *American Journal of Bioethics* now devotes three issues a year. Four topics garnered significant attention in 2007: commercialization of lie detection, deep brain stimulation for the treatment of depression, genetic studies of addiction, and brain imaging. Here we are seeing unanticipated and thorny consequences of the development of new technologies for the diagnosis and treatment of brain disorders. This comes at the same time as remarkable advances in stem cell biology, which may free us from many of the controversies around the use of stem cells from human embryos.

Meanwhile, interactions between the immune system and the nervous system are becoming more tangible. In no case is this more evident than with multiple sclerosis, a disorder in which genetic and environmental factors influence the immune system's attack on the myelin sheath surrounding many nerve cells. Recent studies have demonstrated a link between several immune-system genes and risk for multiple sclerosis. Fascinating recent findings suggest an important link between vitamin D, sun exposure (which increases vitamin D), the immune system, and multiple sclerosis. The immune system may also be important in understanding some chronic pain syndromes.

The mechanisms that produce chronic pain syndromes are mysterious, and they may include maladaptive responses to injury that outlast the initial insult. Because significant chronic pain is so debilitating and often difficult to treat effectively, new insights into the organization and function of pain pathways are required, and new kinds of treatments particularly welcome. This is especially the case as researchers try to provide alternatives to long-term use of opioid drugs, with their potential for becoming addictive. Among the most promising new treatments now under study are neurostimulation, with electrodes implanted either near the spinal cord or peripherally. These methods are intended to use direct stimulation to block the pain signals before they reach the brain. Elsewhere, fascinating new studies provide insight into how the brain produces fever in response to infection,[3] again drawing on our new understanding of

basic cellular signaling mechanisms and our ability to genetically manipulate these in animal models.

Sadly, the major psychiatric disorders, such as schizophrenia, depression, and addiction, first manifest in many individuals when they are adolescents and young adults, at a time when they should be ready and able to enter and contribute to society creatively and independently. Research in 2007 is contributing to a paradigm shift in the understanding of these disorders.

For a long time scientists had focused on the search for single biochemical and molecular causes. Now we understand that thought and mood disorders could be a consequence of faulty connectivity in brain circuits, even if each neuron is functioning correctly. New imaging techniques and genetic manipulations are enhancing the search for genes that play a role in the establishment and maintenance of appropriate circuit structure under a variety of environmental conditions. Moreover, this change in paradigm should support investigation into a variety of new ways of treating these disorders. It will also help us understand the kinds of cognitive disorders that result from loss of specific components of circuits as neurons die in neurodegenerative diseases, such as Alzheimer's disease.

One of the biggest difficulties in treating psychiatric disorders is the extreme heterogeneity of the population, and one of the biggest hopes for the future is that the choice of drug or other treatment will be made with knowledge of the likelihood that the treatment will be effective for that individual, on the basis of his or her genetic makeup.

Many young scientists are drawn to the field of neuroscience by fascination with its really "big" questions, such as the nature of consciousness, the structure of human thought, and the relationship between specific brain structures and our ability to use language, appreciate music, and relate to others. Work in 2007 brings us closer to understanding how the brain, composed of circuits of neurons, actually functions during complex cognitive acts.

Despite the extraordinary insights into brain function in health and disease, each new finding only makes it clearer how much remains to be understood. For example, we all experience mental fatigue, but we haven't a clue what the biological correlates of mental fatigue are. We all know that each person's brain is different, that each of us has stored different memories and uses those to respond uniquely to each other and to the world. At the same time, we believe that the essential

rules by which our brains operate are conserved, most of them not only in the human population but across the animal kingdom. How we understand our individual human attributes in the context of our shared sets of biochemical, molecular, and genetic mechanisms is the major challenge for future work.

ARTS AND COGNITION:
FINDINGS HINT AT RELATIONSHIPS

by Michael S. Gazzaniga, Ph.D.

In 2004, the Dana Arts and Cognition Consortium brought together cognitive neuroscientists from seven universities across the United States to grapple with the question of why arts training has been associated with higher academic performance. Is it simply that smart people are drawn to "do" art—to study and perform music, dance, drama—or does early arts training cause changes in the brain that enhance other important aspects of cognition?

The consortium can now report findings that allow for a deeper understanding of how to define and evaluate the possible causal relationships between arts training and the ability of the brain to learn in other cognitive domains.

The research includes new data about the effects of arts training that should stimulate future investigation. The preliminary conclusions we have reached may soon lead to trustworthy assumptions about the impact of arts study on the brain; this should be helpful to parents, students, educators, neuroscientists, and policymakers in making personal, institutional, and policy decisions.

Specifics of each participating scientist's research program are detailed in the appended reports, which can be downloaded from www.dana.org. Here is a summary of what the group has learned:

1. An interest in a performing art leads to a high state of *motivation* that produces the *sustained attention* necessary to improve performance and the training of attention that leads to improvement in other domains of cognition.

2. Genetic studies have begun to yield candidate genes that may help explain individual differences in interest in the arts.

3. Specific links exist between high levels of music training and the ability to manipulate information in both working and

long-term memory; these links extend beyond the domain of music training.

4. In children, there appear to be specific links between the practice of music and skills in geometrical representation, though not in other forms of numerical representation.

5. Correlations exist between music training and both reading acquisition and sequence learning. One of the central predictors of early literacy, phonological awareness, is correlated with both music training and the development of a specific brain pathway.

6. Training in acting appears to lead to memory improvement through the learning of general skills for manipulating semantic information.

7. Adult self-reported interest in aesthetics is related to a temperamental factor of openness, which in turn is influenced by dopamine-related genes.

8. Learning to dance by effective observation is closely related to learning by physical practice, both in the level of achievement and in the neural substrates that support the organization of complex actions. Effective observational learning may transfer to other cognitive skills.

The foregoing advances our knowledge about the relationship between arts and cognition. These advances constitute a first round of a neuroscientific attack on the question of whether arts training changes the brain to enhance general cognitive capacities. The question is of such wide interest that, as with some organic diseases, insupportable answers gain fast traction and then ultimately boomerang.

This is the particular difficulty of correlations; the weakness and even spuriousness of some correlational studies led to the creation of the consortium. *Correlation* accompanies, parallels, complements, or reciprocates, and is interesting to observe, but only an understanding of mechanisms drives action and change.

Although scientists must constantly warn of the need to distinguish between correlation and causation, it is important to realize that neuroscience often begins with correlations—usually, the discovery that a certain kind of brain activity works in concert with a certain kind of behavior. But in deciding what research will be most productive,

it matters whether these correlations are loose or tight. Many of the studies cited here tighten up correlations that have been noted before, thereby laying the groundwork for unearthing true causal explanations through understanding biological and brain mechanisms that may underlie those relationships.

Moreover, just as correlations may be tight or loose, causation may also be strong or weak. Theoretically, we could claim a broad causation, akin to "smoking causes cancer," with randomized prospective trials showing that children taking arts training can improve certain cognitive scores. Yet, even such a clear-cut result would be weak causation, because we would not have found even one brain mechanism of learning that could suggest progress in *understanding* such mechanisms to guide optimal arts exposure. Nor would we have found by what mechanisms the brain generalizes that learning, or anything about developmental periods during which the brain is particularly sensitive to growth from specific types of experience.

A vast area of valuable research lies between tight correlation and hard-evidence-based causal explanations. Theory-driven questions using cognitive neuroscience methods can go beyond efficacy-of-outcome measures by framing experiments that demonstrate how changes in the brain, as a result of arts training, enrich a person's life and how this experience is transferred to domains that enhance academic learning. Such mid-ground studies would significantly advance our knowledge even though they are not at the level of cellular or molecular explanations.

The consortium work on dance is a good example. Our research indicates that dance training can enable students to become highly successful observers. We found that learning to dance merely by watching can be highly successful and that the success is sustained at the neural level by a strong overlap between brain areas that are used for observing actions and also for making actual movements. These shared neural substrates are critical for organizing complex actions into sequential structure. In the future we can test whether this skill in effective observation will transfer to other academic domains.

Nailing down causal mechanisms in the complex circuitry of the brain is a tall order. The arts and cognition studies by the Dana consortium during the past three years laid a foundation for understanding the mechanisms needed for action; we believe they offer the validity essential for the future studies that will build on them.

A life-affirming dimension is opening up in neuroscience; to

discover how the performance and appreciation of the arts enlarge cognitive capacities will be a long step forward in learning how to learn better and how to live more enjoyably and productively. We offer several suggestions for extensions of the research reported herein:

1. Previous work has established that different neural networks are involved in various forms of the arts, such as music, visual arts, drama, and dance. Future studies should examine the degrees to which these networks are separate and overlap.

2. We also require evidence of how high motivation to pursue an art form will lead to more rapid changes in that network, and we must find out to what degree such changes may influence other forms of cognition.

3. The links between music and visual arts training and specific aspects of mathematics such as geometry need to be more profoundly explored with advanced imaging methods.

4. The link between intrinsic motivation for a specific art (e.g., music and visual arts) and sustained attention to tasks involving that art needs to be followed up with increased behavioral evidence and imaging methods that can demonstrate that changes in specific pathways are greater for higher levels of motivation.

5. The search for individual indicators of interest in and influence by training in the arts should continue to be examined by a combination of appropriate questionnaire research, use of candidate genes already identified, and whole genome scans.

Further research also should pose these questions:

1. To what degree is the link between music training, reading, and sequence learning causative? If it is causative, does it involve shaping connectivity between areas of the brain network involved?

2. Is the link between music and drama training and memory methods a causative one? If so, can we use brain imaging to determine the mechanism?

3. What is the role of careful observation and imitation in the performing arts? Can we prepare our motor system for complex dance movements by simply observing or imagining

desired movements? Do the discipline and the cognitive skill to achieve this goal transfer?

The consortium's accomplishments to date have included bringing together some of the leading cognitive neuroscientists in the world to sort out correlative observations on the arts and cognition and to begin the analysis of whether these relationships are causal. The consortium's new findings and conceptual advances have clarified what now needs to be done. The specific suggestions noted above grow out of the project's efforts—and surely others are possible as well. These suggestions represent a further deepening of a newly accessible field of investigation. Fresh results as well as new ideas are presented herein on how to continue to research this topic.

In my judgment, this project has identified candidate genes involved in the predisposition to the arts and has also shown that cognitive improvements can be to specific mental capacities such as geometric reasoning; that specific pathways in the brain can be identified and potentially changed during training; that sometimes it is not structural brain changes but rather changes in cognitive strategy that help solve a problem; and that early targeted music training may lead to better cognition through an as yet unknown neural mechanism. All of those findings are rather remarkable and challenging.

THE EXPANDING POTENTIAL OF DEEP BRAIN STIMULATION

by Mahlon R. DeLong, M.D., and Thomas Wichmann, M.D.

Introduction

During the last century, largely due to the absence of effective medical treatments, neurosurgeons, concerned to help desperate patients with disabling Parkinson's disease, tremor, and other movement disorders, began to explore the effects of lesioning various brain structures. This practice reached a peak in the 1950s and 1960s, about the same time at which surgery for various psychiatric disorders and abnormal behavior was also peaking. After the introduction of levodopa replacement therapy for Parkinson's in the 1960s, and in response to the strong public outcry against the excesses of psychosurgery, the use of neurosurgical interventions sharply declined during the following decades.

Against this backdrop, it may seem surprising that in the past decade there has been a virtual renaissance of neurosurgical treatments for both neurological and psychiatric disorders. The most fundamental factor accounting for the resurgence of neurosurgical interventions has been the remarkable progress in basic science research into the organization of the motor system and the neurobiology of disorders such as Parkinson's disease. This research, carried out in primate models, has demonstrated that movement disorders such as Parkinson's are the result of abnormal activity in discrete brain circuits, and that modulation of activity in these circuits through highly focused surgical interventions at several nodal points can effectively alleviate symptoms.[1]

Momentum for the resurgence of neurosurgical approaches comes

from several factors: the available medications are not effective in treating all of the patient's symptoms in advanced stages of many of these chronic neuropsychiatric disorders or they have unacceptable side effects, public awareness of the burden of these disorders on patients and their caregivers has increased, and, especially with respect to psychiatric conditions, patient consent procedures and other protections of patient rights are now consistently used.

Most of the targets for functional neurosurgical procedures that are in use today involve a cluster of brain structures called the basal ganglia. These subcortical brain structures are viewed as components of a family of anatomically distinct brain circuits that also encompass the cerebral cortex and thalamus. These circuits subserve aspects of motor behavior ("motor circuit"), cognitive/behavioral function ("associative circuit"), and emotion and motivation ("limbic circuit").

Broadly speaking, movement disorders such as Parkinson's result from abnormal neuronal activity in the motor circuit, while abnormalities in limbic or associative circuits may underlie some of the symptoms and signs of neuropsychiatric conditions. Consequently, surgeries in movement disorder patients are generally aimed at targets within the motor circuit, while neuropsychiatric diseases are being treated with interventions aimed at the limbic or associative circuit.

In the new generation of surgical approaches, deep brain stimulation (DBS) stands out for its ability to spark changes in the activity of certain circuits. DBS was first explored for movement disorders in the late 1970s as a treatment for tremor and was later found to be also highly effective for Parkinson's disease and other movement disorders as more suitable targets were identified. In contrast to the irreversible effects of lesioning approaches, the brain is not permanently altered by DBS but is modified by the local application of electrical current in a way that can be changed or even reversed.

During DBS surgery, stimulating electrodes with four different contacts are implanted into specific brain regions, and a programmable pulse generator is implanted under the skin below the collarbone, similar to a cardiac pacemaker. The pulse generator can be programmed to deliver continuous stimulation of the optimal frequency, amplitude, and pulse duration to the targeted brain region. Reversibility and adjustability of stimulation are major advantages of DBS, as is its focused application in the relevant targets, which reduces the adverse side effects seen with drugs that act widely in

the brain.

Deep brain stimulation offers truly remarkable benefits to patients with advanced movement disorders and other conditions, but exactly why it works remains unclear. Scientists first believed it simply mimicked the effects of lesioning, but more recent studies of brain activity in animals and patients have suggested that DBS alters patterns of activity in the extended brain networks associated with the stimulated brain region by activating axons that leave or enter the stimulated region of the nucleus.

Movement Disorders

The most common application of deep brain stimulation is for patients with advanced Parkinson's disease, a progressive disorder characterized by slowness of movement, tremor, and muscular rigidity. The symptoms are caused by the loss of the neurotransmitter dopamine in the basal ganglia, which strongly affects the neuronal activity throughout the motor circuit.

While the early stages of Parkinson's are amenable to medical therapy, the development of drug-induced involuntary movements called dyskinesias and the more rapid wearing off of medication limit the effectiveness of medication treatments in later stages of the disease. DBS within the motor portions of two basal ganglia nuclei, the subthalamic nucleus and the internal segment of the globus pallidus, reverses many of the motor problems of Parkinson's, as well as the drug-induced complications.[2,3] Major surgical complications are infrequent, occurring in 1 to 2 percent of patients, and the long-term benefits are substantial.

In addition to the subthalamic nucleus and globus pallidus, several alternative DBS targets are currently being explored, for instance the pedunculopontine nucleus, which shows some promise for severe cases of Parkinson's disease with treatment-resistant gait and balance problems. DBS is also being used successfully in patients with movement disorders other than tremor and Parkinson's. For example, stimulation is now being tested in a variety of forms of dystonia, a highly variable movement disorder characterized by generalized or focal involuntary twisting movements and abnormal postures, bringing new hope to individuals who respond poorly to currently available treatments.[4]

Neuropsychiatric Disorders

Because of the remarkable success of deep brain stimulation for Parkinson's disease and other movement disorders and the insight that several common neuropsychiatric conditions may be caused by similarly abnormal activity patterns in neuronal networks, neurosurgeons are now beginning to cautiously explore the use of DBS for several such conditions. At present, these procedures remain strictly experimental.

One promising area is the treatment of obsessive-compulsive disorder (OCD), a condition characterized by the presence of intrusive thoughts and compulsive behaviors. Neurosurgical lesioning treatments for OCD have traditionally been aimed at empirical targets, such as the anterior limb of the internal capsule. It has recently been reported that DBS at the same target[5] or in the nearby ventral striatum may also be beneficial.

Tourette's syndrome, in which involuntary rapid, stereotyped movements and vocalizations (motor and vocal tics) are often associated with OCD, attention-deficit/hyperactivity disorder, depression, and psychosocial difficulties, may also be treatable with DBS.[6] Because symptoms often remit after adolescence, treatment is reserved for severe cases that have not improved spontaneously. Based on earlier empirical lesion studies and consideration of the relevant limbic circuit anatomy, DBS at several surgical targets has been tested in these patients, including the midline intralaminar thalamic nuclei or the motor and limbic portions of the globus pallidus. The preliminary studies have demonstrated substantial symptomatic benefits in some cases.

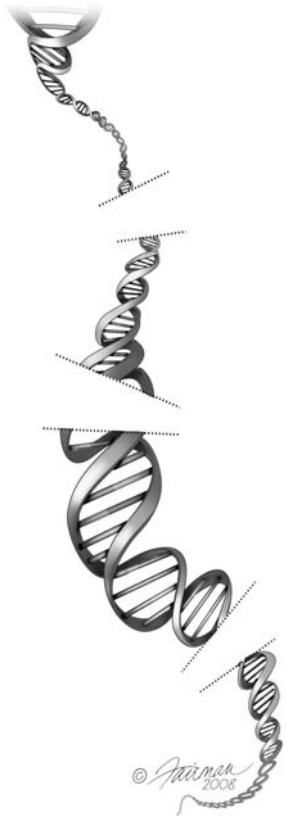
Several studies are also now under way to evaluate the potential of DBS in patients with severe depression that is unresponsive to conventional therapies. Following imaging studies suggesting that the cortical subgenual cingulate region, also called area 25, may be a key structure in depression, a recent study reported that DBS in this area produces significant clinical benefits in patients with depression.[7] With prolonged stimulation (for six months) a significant and sustained improvement was reported in two-thirds of the subjects, all of whom had failed multiple treatment trials. Needed now are follow-up studies and larger, well-controlled trials to try to confirm these findings and to gather data on other targets, such as the ventral striatum.

Conclusions

Deep brain stimulation has become the neurosurgical procedure of choice for patients with disabling movement disorders and is currently also being explored for patients with a variety of severe neuropsychiatric disorders. Although the neurobiological bases of disorders such as OCD, Tourette's syndrome, and depression are less well understood than those of movement disorders, a common element between these conditions seems to be that they are associated with brain circuit dysfunction, for which DBS may prove to be effective in patients with treatment-resistant symptoms.

PROGRESS IN BRAIN RESEARCH IN 2007

DISORDERS THAT APPEAR IN CHILDHOOD



In 2007, scientists identified some of the genetic bases of autism spectrum disorders and attention-deficit/hyperactivity disorder—two of the most common developmental disorders. Researchers also began to lay the foundations for finding a potential cure for Rett syndrome, the most physically disabling of the autism spectrum disorders, with which mostly girls are diagnosed because few boys survive past age 2, as well as fragile X syndrome, the most common inherited form of mental retardation, which occurs primarily in boys.

The Genetics of Autism

Although studies in twins have shown that autism spectrum disorders are highly heritable, researchers have not been able to identify strong autism gene candidates so far. Moreover, the majority of people with autism have no family history of the disease, suggesting that inherited risk factors are quite complex. But in 2007, a team of scientists led by Jonathan Sebat of Cold Spring Harbor Laboratory was able to gain some new insights into the genetics of these disorders.

In a paper published in *Science* in April, Sebat and colleagues reported that gene mutations called copy number variations, not present in either parent, appear to create a greater risk for autism than had been thought previously.[1] These mutations typically involve deletions of tiny gene segments that arise spontaneously, rather than being inherited.

Sebat's team looked for copy number variations in 264 families, including 118 "simplex" families with a single child with autism, 47 "multiplex" families with multiple affected siblings, and 99 control families with no diagnoses of autism.

The investigators found that, among children with autism spectrum disorders who had no siblings with a disorder, 10 percent had gene-segment deletions, compared with 2.6 percent of children with autism spectrum disorders from multiplex families and 1 percent of the controls. These deletions occurred at many different sites in the genome. These data support the notion that spontaneously arising mutations in many genes are involved, and may in part explain why findings from previous genetic studies were inconsistent.

The fact that many genes may be involved in a disorder also suggests something fundamental about autism: perhaps the common features of autism (impaired social interaction, difficulty with communication,

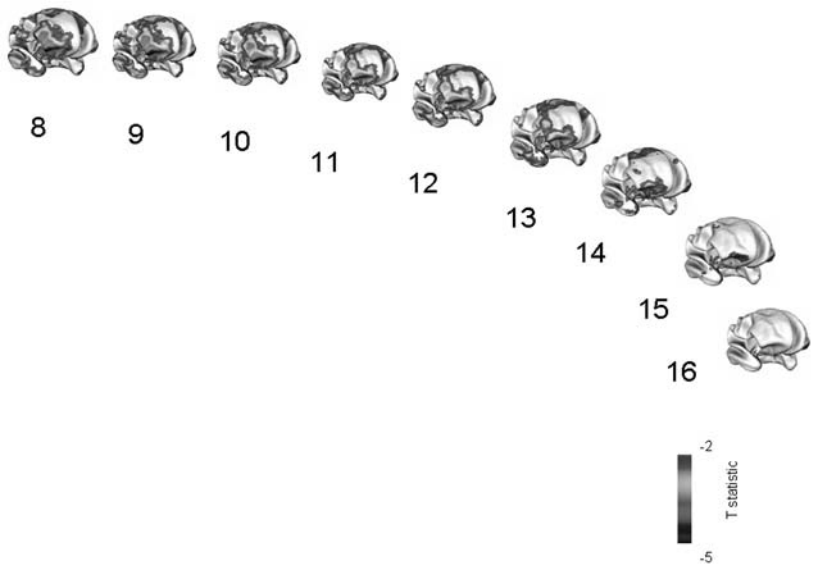
and restricted interests and behaviors) owe their "commonality" not to common genes but to a common biological pathway involving a large and diverse set of genes.

The findings also have implications for the clinic. By screening children with autism spectrum disorders for spontaneous mutations, clinicians may be able to inform the parents about their risk of having a second child with an autism spectrum disorder—which is thought to be lower if a spontaneous mutation is present.

Attention-Deficit/Hyperactivity Disorder

Attention-deficit/hyperactivity disorder is characterized by several features: it is very common (affecting 3 to 7 percent of children), it is highly heritable, and it tends to ease in affected children as they get older. And a 2007 study may have homed in on one gene associated with the improvement in older children.

In a study published in August in *Archives of General Psychiatry*, Philip Shaw and colleagues at the National Institute of Mental Health investigated the effects of one of the most important known genetic risk factors for the disorder.[2] The researchers studied a gene that



Children with attention-deficit/hyperactivity disorder have a thinner cortex than those without, but brain scans (in which the numbers note the child's age) show that, in the 30 percent of cases where ADHD is associated with a certain rare genetic variant, this gap is resolved by about age 16.

is one of the rarer forms of the receptor for the neurotransmitter dopamine, called D4. Unlike other dopamine receptors, this receptor has a 7-repeat variant in a part of the gene called axon 3. This genetic variant accounts for about 30 percent of inherited cases of the disorder, making it by far the strongest candidate gene.

The researchers collected DNA, clinical data, and brain magnetic resonance images for 105 children with attention-deficit/hyperactivity disorder (ADHD) and 103 children without the disorder. An analysis of the data showed that, among children with attention-deficit/hyperactivity disorder, possession of the 7-repeat gene was associated with both better clinical outcome and higher intelligence compared with children who did not have the 7-repeat gene. These findings were highly specific: no similar association with either a clinical outcome or a distinctive trajectory of cortical development was found with two other known genetic risk factors for ADHD.

The investigators also found that children who had the 7-repeat variant of this gene showed a distinctive pattern of cortical development: the thickness of the cortex in areas important for the control of attention was initially thin, but then it thickened, converging with the development path of the healthy children by about age 16.

In a previous study, the same group of researchers reported that this pattern of cortical development was associated with better clinical outcomes in attention-deficit/hyperactivity disorder. The 2007 study linked genetics with both clinical outcome and cortical development, and it raises the hope that in the future, such genetic information could guide treatment efforts by clinicians.

Rett Syndrome Progress

Rett syndrome, caused by mutations in the gene methyl-CpG-binding protein 2 (MeCP2), affects primarily girls. Symptoms develop in early childhood, resulting in impairments in speech, normal movement, and hand use. Disordered breathing patterns and Parkinson's-like tremors are common.

Females with Rett syndrome have one mutated and one normal MeCP2 gene. Therefore, female mice with a stopped gene on one X chromosome are the best genetic model for this disorder. These mice develop Rett-like symptoms, such as tremors and problems with mobility and gait, between 4 and 12 months of age, and they then remain chronically symptomatic for an apparently normal life span.

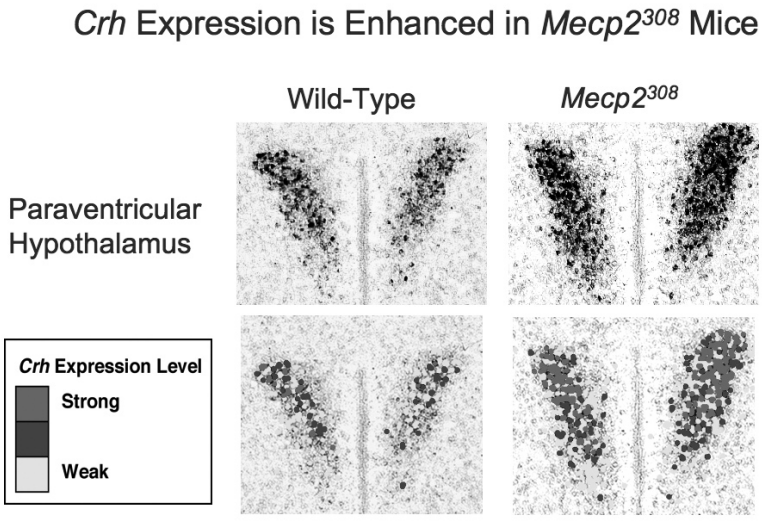
Adrian Bird, with colleagues at the Wellcome Trust Centre for Cell Biology in Scotland, manipulated the production of a protein called MeCP2 in a mouse model of Rett syndrome. They found that restoring MeCP2 production reversed symptoms.

Although neurons show fewer branches than normal, there is no evidence for nerve cell death in either the mouse model or Rett patients (unlike neurodegenerative disorders such as Parkinson's, Huntington's, or Alzheimer's disease). Because the faulty neurons remain alive, researchers at the Wellcome Trust Centre for Cell Biology at Edinburgh University in Scotland wondered whether restoring normal MeCP2 protein could rescue the nerves' function and "cure" the mice.

In a study published in February in *Science*, Adrian Bird and colleagues tested this hypothesis by introducing a "stop-cassette" into the mouse MeCP2 gene, which prevented it from making MeCP2 protein.[3] The stopped gene could be reactivated at will by injecting the mouse with the drug Tamoxifen, which set in motion a sequence of molecular events culminating in deletion of the stop-cassette, thereby reactivating the MeCP2 gene to produce the protein.

The scientists waited until full-blown symptoms had developed in female mice before administering Tamoxifen. Strikingly, restoration of the MeCP2 gene to produce MeCP2 protein eradicated tremors and normalized breathing, mobility, and gait in mice that were sometimes only days away from death. In addition, female mice also recovered electrophysiological function, as measured by the ability of nerve cells to respond to stimulation.

Investigators also tried Tamoxifen in male mice after symptoms had developed. Again, most or all symptoms disappeared in male



Mutations in the protein MeCP2 cause Rett syndrome. Mice bred with these mutations show elevated levels of a stress-control hormone called corticotrophin releasing hormone (CrH) in the hypothalamus, which is likely to contribute to the stress and anxiety that are Rett features.

mice with a restored MeCP2 gene, and these mice survived for an apparently normal life span.

These findings imply that the symptoms of Rett syndrome are potentially reversible, which may inspire similar research in related autism spectrum disorders.

Important Enzyme in Fragile X

A research group led by Nobel laureate Susumu Tonegawa at the Massachusetts Institute of Technology obtained similarly encouraging results regarding fragile X syndrome, the most common inherited form of mental retardation, which occurs primarily in males. Their research was published in the July *Proceedings of the National Academy of Sciences*.[4]

In the study, mice with a model of fragile X syndrome exhibited symptoms similar to those in human patients: hyperactivity, repetitive movements, attention deficits, and difficulty with learning and memory tasks.

The experimental animals also had structural abnormalities that were similar to those found in humans. These males have a high number of dendritic spines in neurons in their brains, but each spine

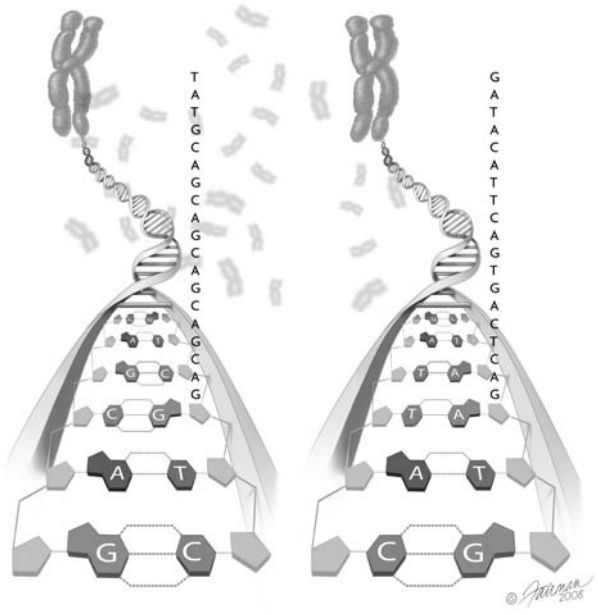
is longer and thinner than normal and transmits weaker electric signals than those in non-affected individuals. Dendritic spines are small protrusions on the branch-like dendrites of neurons that receive chemical signals from other neurons and communicate them to the main cell body.

The scientists hypothesized that inhibiting a certain enzyme in the brain could be an effective way to counter these structural changes, as well as the debilitating symptoms of fragile X syndrome. The enzyme, called p21-activated kinase, affects the number, size, and shape of connections between neurons in the brain.

The researchers found that halting the enzyme's activity reversed the structural abnormality of neuronal connections in mice. Moreover, inhibiting the enzyme restored electrical communication between neurons in the brains of the mice, correcting their behavioral abnormalities in the process.

Because the expression of the gene that inhibits p21-activated kinase occurs after birth, it is possible that chemical compounds that inhibit the enzyme's activity could one day be used to prevent or reverse mental impairments in young children with fragile X syndrome.

MOVEMENT DISORDERS



Research into Huntington's disease and Parkinson's disease in 2007 brought the genetic and molecular underpinnings of these movement disorders more clearly into view but also revealed their dazzling complexity, thereby tempering excitement about treatment advances. Deeper understanding of both diseases depends on greater insights into the molecular activity taking place within brain cells, researchers say.

Huntington's Disease

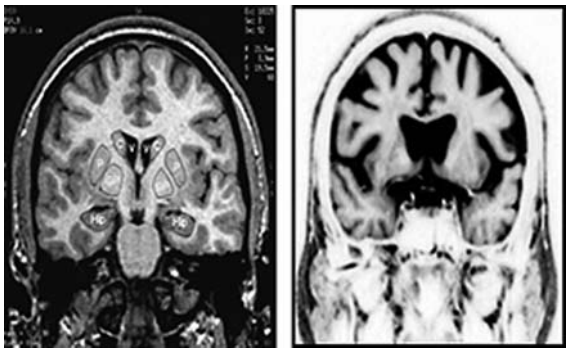
People who develop Huntington's disease are born with the gene mutation that causes the disease, but many do not develop symptoms until they are in their forties. This long lag has puzzled scientists, but explanations have begun to emerge.

In one of the most provocative insights into Huntington's disease during 2007, Cynthia T. McMurray and colleagues at the Mayo Clinic and elsewhere traced the disease process to the routine oxidation and repair of DNA, which has long been known to play a key role in the aging process itself.

Throughout life, oxygen atoms attach to nucleotides in the ribbon of DNA in each cell. Enzymes in the cell snip out those oxidized fragments and repair the DNA. In a paper in *Nature*, McMurray demonstrates that in people who carry the Huntington's disease mutation, this process results in an expansion of the number of repeats of a sequence of three bases—cytosine, adenine, and guanine (CAG)—present at birth on chromosome 4.[1] This sequence provides instructions for the manufacture of the huntingtin protein, crucial for transporting neurotransmitters from the cell body down the axon to the synapse, where communication between cells takes place.

Normally, people have between 10 and 35 CAG repeats on chromosome 4. People who have 40 or more CAG repeats eventually develop symptoms of Huntington's, and the greater the number of repeats, the earlier symptoms tend to appear. For example, a child with 95 repeats developed seizures, cognitive decline, and neuromuscular disorders by the age of 3 and died of Huntington's disease at age 11.

The normal repair of DNA tends to increase the number of CAG repeats, according to McMurray. She blames this effect on a single enzyme known as OGG1, which causes neurons to produce an increasingly toxic form of the huntingtin protein containing too



Brain scans show the dramatic difference between a healthy individual (left) and one with Huntington's disease (right).

much glutamine, an amino acid crucial for cell metabolism. The extra glutamine makes the huntingtin protein sticky, causing it to clump together and create debris within the nucleus. This leads to a cascade of cell dysfunction that eventually produces the symptoms of Huntington's disease.

This observation coincides with the linear relationship between the number of CAG repeats and the age of disease onset. Those born with a large number of CAG repeats develop symptoms early, whereas those born with a smaller number of repeats do not develop symptoms until this DNA repair process has had time to expand the number of CAG repeats to a more toxic level.

In mice that lack the OGG1 enzyme, CAG expansion was powerfully suppressed with no ill effects, suggesting that DNA repair could be carried out by "backup" enzymes. Thus, this enzyme appears to be specifically responsible for promoting CAG expansion, suggesting that if OGG1 somehow could be blocked in humans, the damage caused by Huntington's disease could be significantly postponed or even prevented.

Taking a different approach, researchers at Cambridge and Harvard have attempted to mitigate the toxic effects of mutant huntingtin protein by coaxing cells to remove toxic debris more efficiently.

In a paper published in *Nature Chemical Biology*, Stuart L. Schreiber, David C. Rubinsztein, and colleagues report that administering what they call "small-molecule enhancers" to yeast stimulates autophagy, a process by which cells dispose of defective and misfolded proteins such as mutant huntingtin.[2] If autophagy could be stimulated in people with Huntington's disease, it would do nothing to slow or stop the production of huntingtin, but by clearing toxic debris from the cells more effectively, it might postpone the onset of symptoms, the researchers believe.

But mutated huntingtin protein appears to cause numerous other problems, which Elena Cattaneo and colleagues at the University of Milan are studying.

For example, normal huntingtin stimulates the production of brain-derived neurotrophic factor (BDNF), a protein that supports existing neurons and encourages the growth of synapses and new neurons. In people with Huntington's disease, neurons in the striatum die, producing spasticity and many other symptoms. In 2001 Cattaneo and colleagues demonstrated that levels of BDNF are known to be lower in people with Huntington's.[3]

Mice with a model of Huntington's disease show a lack of cholesterol, and researchers attribute this deficiency to the same mutant huntingtin protein found in people with Huntington's.

In 2007, they expanded on that discovery by attributing the dysfunction to a genetic regulatory site that affects BDNF in people with Huntington's disease.[4] However, the site is located in a region of more than 1,000 genes that affect more than just BDNF, suggesting that other genes that affect neurons may be dysfunctional in people with Huntington's. Currently Cattaneo's team is looking for molecules that will mimic the activity of normal huntingtin and increase the expression of BDNF and related genes. So far they have identified three compounds that increase the production of BDNF in cells affected by Huntington's disease.[5]

BDNF also appears to regulate the development of synapses by increasing the amount of cholesterol in synaptic vesicles.[6] In 2005, Cattaneo and colleagues found that cells and tissues in people with Huntington's had too little cholesterol and that adding cholesterol to the striatal neurons most affected by the disease prevented their death.[7] In a 2007 paper in *Human Molecular Genetics*, Cattaneo and colleagues report that mice with a model of Huntington's disease also show a lack of cholesterol, and they attribute this deficiency to the same mutant huntingtin protein found in people with Huntington's.[8]

The researchers suspect that BDNF signaling directly affects cholesterol biosynthesis, a hypothesis that unifies two seemingly separate dysfunctions.

And while a cure for Huntington's disease must await a form of genetic engineering that will fix the DNA repeats that result in

faulty huntingtin protein, a recent study in mice found that a small molecule known as C2-8 may inhibit the aggregation of mutant huntingtin within cells, which would at least slow the development of symptoms.[9]

Parkinson's Disease

Researchers developed two novel ways to treat Parkinson's disease in 2007, raising hopes of at least alleviating symptoms such as tremors and muscle rigidity.

Researchers at Northwestern University reported in *Nature* that they could "rejuvenate" dopamine-producing neurons in a brain region called the substantia nigra pars compacta. These neurons die in people with Parkinson's, thereby depriving the brain of enough neurotransmitter to maintain normal movement.[10]

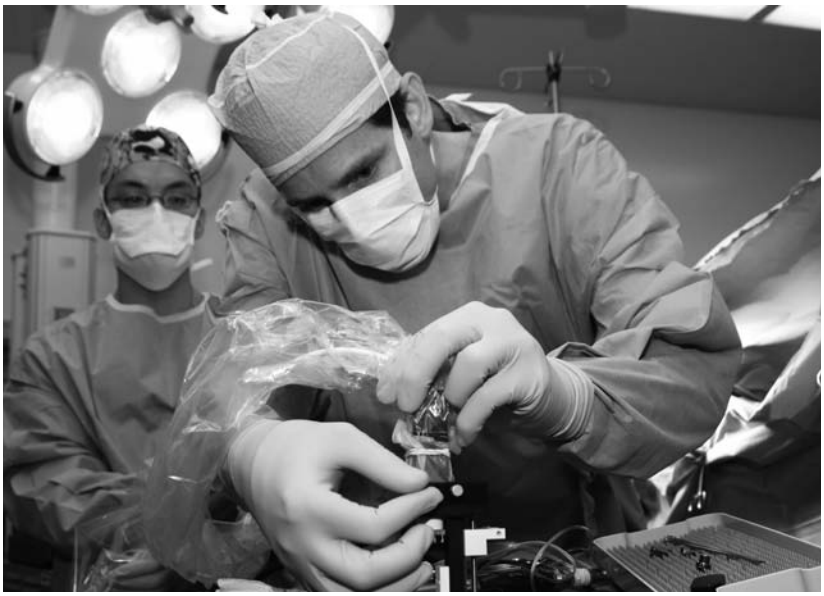
These cells ordinarily use calcium channels to maintain normal metabolism. However, James Surmeier and colleagues found that mice bred without calcium channels functioned normally because their dopamine-producing cells continued to use their sodium channels, which are normally active only in youth.

They applied isradipine, a calcium channel inhibitor, to block the calcium channels in neurons taken from normal mice. For about 30 minutes the cells ceased functioning. Then they resumed their pacemaking activity as the dormant sodium channels began functioning again. When the researchers implanted pellets of isradipine below the skin in mice bred to have symptoms of Parkinson's disease, the mice did not develop the motor deficits characteristic of the disease.

Further evidence that isradipine may be helpful comes from the fact that it belongs to a class of drugs used to treat hypertension. A retrospective study suggests that patients with hypertension treated with these drugs have a lower incidence of Parksinson's.[11]

A failure of the mitochondria, the energy-producing vesicles inside of cells, is another possible cause of the breakdown of dopamine-producing neurons. Researchers at Stanford showed that a mutation in a gene known as pink1 correlates with a higher incidence of Parkinson's disease.[12] When they bred fruit flies with this mutation, the fruit flies' flight muscles, as well as their dopamine-producing neurons, degenerated.

The muscle degeneration was preceded by abnormalities in the mitochondria, which produce energy for the cell. Mitochondrial



Yu-Hung Kuo, left, watches as Michael Kaplitt of New York–Presbyterian Hospital/Weill Cornell Medical Center prepares to infuse an enzyme in hopes of improving movement in patients with Parkinson's.

dysfunction has been suspected in Parkinson's disease, the authors say, because pesticides known to increase the risk of the disease inhibit mitochondria. However, flies bred to overexpress parkin, a protein involved in the clearing of misfolded proteins, did not develop these problems, suggesting that pink1 and parkin operate in a common pathway that regulates mitochondrial function and cell survival in fruit flies.

In the realm of treatment, research in 2007 suggested hope for gene therapy. In the first gene therapy study for Parkinson's, it produced significant improvement with no ill effects.[13] Researchers at New York–Presbyterian Hospital/Weill Cornell Medical Center implanted a harmless virus bearing a gene for an enzyme called glutamic acid decarboxylase (GAD) into 12 patients. GAD produces GABA, a neurotransmitter that quells excessive neuronal firing and promotes coordinated movements.

The harmless, GAD-bearing virus was implanted in the subthalamic nucleus at the center of the brain, which regulates movement, in hopes of boosting the production of GABA and thereby restoring normal function, according to lead author Michael Kaplitt. (In 2003, Kaplitt performed the world's first gene therapy surgery for Parkinson's.)

To minimize possible risk, the harmless virus was implanted in only one side of the brain, but because patients have symptoms on both sides of their body equally, this technique also provided a way to recognize and measure improvement. Three months after the surgery the patients as a group showed a 25 to 30 percent improvement in movement according to the Unified Parkinson's Disease Rating Scale. Some showed improvement of 40 to 65 percent.

Such impressive improvement puts interest in this potential therapy in the company of deep brain stimulation, which is already widely used to control the gait disturbances and movement problems of Parkinson's disease (see also Neuroethics, page 45) in patients to extend the window of therapeutic effectiveness.

Deep brain stimulation holds out the greatest immediate promise for Parkinson's patients. The therapy involves implanting electrodes deep within the brain, in a region called the subthalamic nucleus. These electrodes are then stimulated to modify electrical communication of nerve cells within and among brain circuits. Through this process, deep brain stimulation blocks the uncontrolled signals that produce the motor symptoms of Parkinson's, especially tremor.

In 2007 researchers in Italy expanded upon deep brain stimulation by placing electrodes in a new area, the pedunculopontine nucleus, that plays an important role in walking.[14] Six patients with Parkinson's who had not responded well to medication safely responded to electrodes that stimulated the pedunculopontine nucleus at 25 Hz and the subthalamic nucleus at 185 Hz. Patients improved overall by more than 60 percent as measured by the rating scale—well above the improvement achieved by stimulation of either brain area alone, or by medication.

Deep brain stimulation is now an approved and accepted therapy in Parkinson's disease patients whose symptoms can no longer be treated with L-DOPA, or whose side effects from long-term L-DOPA medication have become debilitating.

For deep brain stimulation, scientists continue to study where in the brain electrodes will alleviate symptoms most effectively. Another recent study found that deep brain stimulation may even have a neuroprotective effect on the dopamine-producing cells in the substantia nigra that degenerate in the disease.[15]

NERVOUS SYSTEM INJURIES

Nervous system injuries comprise a diverse group of disorders affecting the brain and spinal cord, including stroke, spinal cord injury, and brain tumors. In 2007, researchers reiterated the importance of acting quickly after stroke, tried new approaches to treating brain tumors, and worked to improve clinical trials in spinal cord injury.

Act Quickly After Stroke

Getting to a hospital in time and getting the right care once there continue to dominate the news in clinical research of stroke, and new data from Europe extend the urgency to the follow-up care of people with transient neurological symptoms as well.

In May, the American Heart Association and the American Stroke Association updated their acute-care guidelines for stroke, reaffirming top billing for tissue plasminogen activator (tPA), the anti-clotting agent that should be given within three hours of stroke onset in order to minimize brain damage after ischemic stroke.[1] (Ischemic stroke is caused by a lack of oxygen to the brain, typically due to a blockage in arteries that feed blood to the brain.) The guidelines also urged better preparedness for rapid response by hospital emergency rooms and first responders; new data from the Centers for Disease Control and Prevention show that fewer than half of stroke patients reach hospitals within two hours of the onset of acute neurological symptoms.[2]

While a major stroke is often marked by overt symptoms, such as blurred vision, slurred speech, or numbness or paralysis in one side of the body, some brain effects of ischemia are temporary and leave no clinically detectable signs. These are referred to as transient ischemic attacks. Brain imaging studies of patients who have had temporary neurological symptoms show evidence suggestive of such transient attacks. Once a transient ischemic attack occurs, the underlying cause likely persists and may eventually cause a major stroke, unless treated appropriately. Transient ischemic attacks, therefore, are important risk factors for major stroke.

Interventions following a transient ischemic attack are aimed at preventing additional strokes in the weeks and months afterward. A large base of evidence now suggests that reducing stroke risk factors, such as high blood pressure and elevated cholesterol, can prevent strokes. Two papers published in October point to the importance of

initiating such therapies immediately in people who have suffered a transient attack.

The first, by neurologist Peter Rothwell and colleagues at the University of Oxford, England, and published in *Lancet*, found that patients who were treated with existing preventative therapies within 24 hours of a transient ischemic attack had a dramatically reduced risk of developing a serious stroke in the next three months, compared with patients who did not receive immediate follow-up care.[3] Specifically, the risk of a recurrent stroke was cut from 10 percent to 2 percent, an 80 percent reduction, which the authors said could translate to the prevention of 10,000 strokes a year in the United Kingdom alone. The study examined about 600 people, drawn from a larger Oxford study that is tracking the incidence of stroke and transient ischemic attack in nearly 100,000 people.

A second study, published in *Lancet Neurology* and led by stroke neurologist Pierre Amarenco of Bichat-Claude Bernard University Hospital in Paris, also affirmed the benefit of early intervention to prevent strokes.[4] The researchers evaluated 1,085 patients with a suspected transient ischemic attack who were admitted to a 24-hour hospital clinic. Urgent assessment included imaging of the brain, blood vessels, and heart. Patients with confirmed or possible transient ischemic attacks were immediately put on a preventative therapeutic regimen, which typically involved drugs to reduce blood pressure and/or cholesterol and aspirin to reduce blood clotting.

About 5 percent of patients underwent procedures to open the carotid artery, the main artery in the neck that feeds blood to the brain. These patients underwent either open surgery (carotid endarterectomy) or trans-arterial placement of a stent to expand the carotid artery (endovascular therapy). Another 5 percent who had atrial fibrillation, a disturbance of the rhythm of the heartbeat, were given anticoagulant drugs to reduce the risk of blood clots forming in the heart due to this condition. Such clots can travel from the heart to the brain and cause a stroke.

Among patients who were treated early, the rate of stroke in the 90-day period after the transient ischemic attack was just over 1 percent, compared to an expected rate of nearly 6 percent based on previous observational studies. Taken together with the Lancet report, the findings prompted experts worldwide to urge a new standard of care for patients suffering transient ischemic attacks, emphasizing urgent assessment and treatment to prevent stroke.

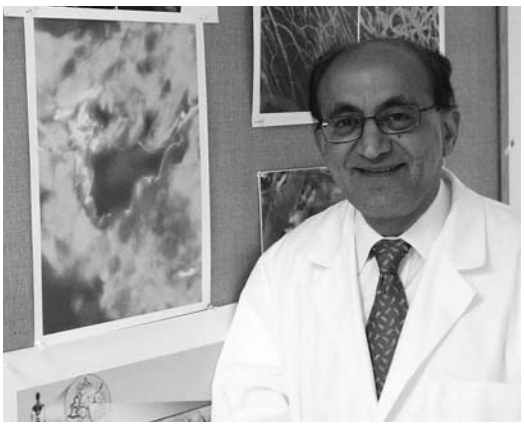
Targeting Brain Tumors with Molecular Precision

While brain tumors continue to evade effective treatment approaches, much of the current anticipation relates to the development of molecularly targeted therapies to attack tumors, as is true in cancer research overall. There is also a growing appreciation that no one therapy may be enough to eradicate the most lethal brain cancers, leading to increasing investigation of combination approaches that add newer therapies to standard treatments such as radiation and chemotherapy.

Many researchers are convinced that such multimodal therapies offer the best hope for people facing a diagnosis of malignant glioma, a family of brain tumors that, though relatively rare, have high death rates within a short period following diagnosis. Glioblastoma multiforme, one of the most aggressive members of this family, has been particularly difficult to treat.

Clinical research in this area is being driven by new understanding about the pathogenesis of tumor development at the molecular level as scientists unravel the specific signaling factors and pathways that tumors use to grow and spread. Differences among tumors are negating a "one-size-fits-all" approach to treatment. Still, there appear to be commonalities in some elements of the pathways tumors use, and researchers are focusing many of their efforts on these common features.

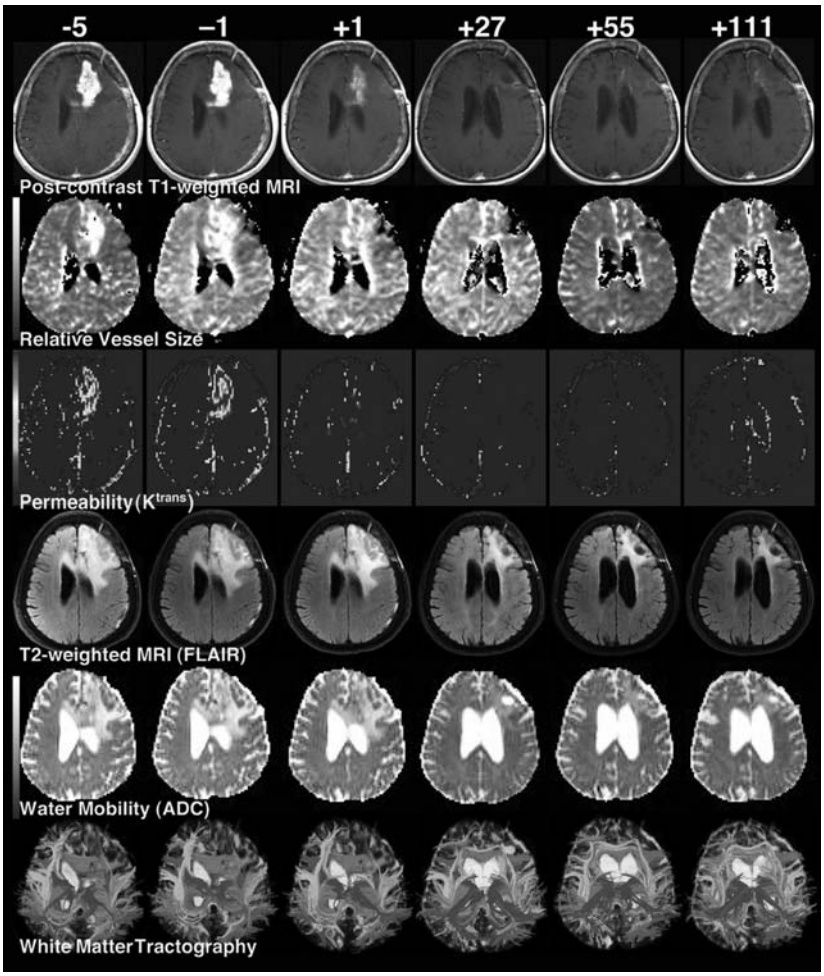
One promising avenue is to starve tumors of their blood supply, an approach that is being investigated for many types of cancer. In January 2007, Rakesh Jain and colleagues from the Massachusetts General Hospital Cancer Center reported preliminary results in



Rakesh Jain and colleagues at Massachusetts General Hospital Cancer Center studied a drug that tamps the growth of brain-tumor blood vessels.

Cancer Cell of an investigational drug that suppresses the growth of blood vessels that feed tumors.[5] This drug, AZD2171, blocks the three primary receptors for VEGF, a powerful blood vessel growth promoter known to be present on vessels that feed glioblastoma tumors. (Mature blood vessels in normal tissue do not rely on VEGF for survival.)

Results from a Phase 2 clinical trial in 16 patients with recurrent glioblastoma who were treated with AZD2171 found that tumors



The experimental drug shows promise in brain scans of the most responsive test patient. The numbers at the top correspond to days before or after starting treatment. The top row shows the tumor shrinking over time. Other rows show drops in tumor blood-vessel size, the permeability of the blood-brain barrier, and swelling in regions around the tumor. The last row shows white matter visibility as swelling subsides.

shrank by 50 percent or more in half of the patients, and by at least 25 percent in three-quarters of the study participants. Brain imaging showed a rapid effect on the normalization of blood vessels, beginning after just one dose of the medication in some patients, and a decrease in brain swelling, a common problem in brain cancer. The trial is continuing, and the researchers hope to also investigate the drug in combination with traditional cancer therapies in people newly diagnosed with glioblastoma.

Brain tumor experts say the key to improving treatment for malignant gliomas lies in better determining which patients are most likely to respond to specific therapies and in improving combinatory approaches to treatment.

Researchers at Duke University have combined another blood vessel inhibitor, bevacizumab (Avastin), with the chemotherapeutic drug irinotecan in a Phase 2 trial of 32 patients with advanced glioma. Preliminary results, published in *Clinical Cancer Research* in February 2007 by James Vredenburgh and colleagues, suggest that the combination is active against this lethal form of tumor and has "acceptable" toxicity.[6] In nearly two-thirds of the patients, tumors shrank by at least 50 percent, and at six months, tumors had not started to regrow in 38 percent of the patients. In contrast, chemotherapy alone typically slows glioma growth for just six weeks to three months.

Vredenburgh and other brain tumor experts say the key to improving treatment for malignant gliomas lies in better determining which patients are most likely to respond to specific therapies and in improving combinatory approaches to treatment. They also point to the need for improving clinical trial designs to obtain the maximum amount of information in the shortest period of time.

Spinal Cord Injury: Paving the Way for Clinical Trials

Better clinical trial design also has been a focus in spinal cord research, as work in this area advances toward the translation of basic science findings into therapeutic approaches. In March 2007, an international multidisciplinary panel of researchers published the

first guidelines for clinical trials in spinal cord injury in a series of four papers in *Spinal Cord*.[7–10]

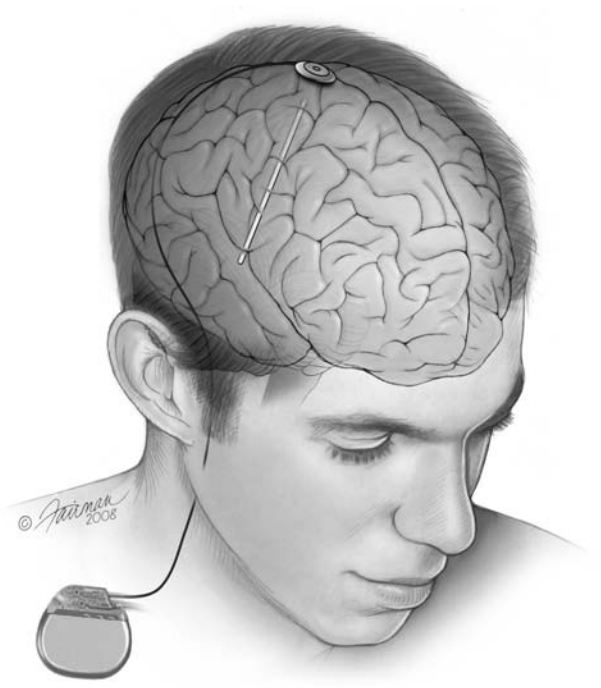
The effort, by the International Campaign for Cures of Spinal Cord Paralysis, is an attempt to delineate criteria for robust, realistic, and useful clinical trials for anticipated therapeutic options that are currently being tested in preclinical investigations. The panel called for rigorous and standardized attention to outcome measures, inclusion and exclusion criteria, and ethics in designing and conducting human research trials.

For example, the authors said that outcome measures should include anatomical and neurologic assessment to demonstrate "reconnection" of the spinal cord, measures of patients' ability to engage in activities of daily living, and quality-of-life measures. With respect to inclusion/exclusion criteria, the panel said that patients participating in studies should be at stages of injury where there are data from animal studies or previous human studies to support a potential benefit of intervention, and that the severity, level, type, and size of their injury should be considered in relation to the likelihood that an experimental treatment would benefit them. Study participants must provide informed consent based on a clear, adequate explanation of the risks, benefits, and scientific rationale of investigational therapies, the authors said.

Prospective, double-blind, randomized trials utilizing appropriate control participants are optimal, the group said, while recognizing that in some situations, other trial procedures may have to be considered.

The guidelines appear to be prompted in part by the frustration of Western scientists trying to evaluate the effectiveness of uncontrolled human research. In a field where no treatment is known to be effective, patients and their families have been desperate for a treatment for spinal cord injury. As a consequence, they and some researchers have been willing to try anything. This has become a particular problem in countries where regulations governing clinical research are lacking, including China, where scores of unproven stem cell transplants are being done in spinal cord–injured patients. The panel also seeks to avoid clinical trial design problems that have plagued the development of treatments for other complex neurological problems—notably the lack of sufficiently sensitive outcome measures in clinical trials investigating new neuroprotective therapies for stroke.

NEUROETHICS



The ethical implications of the many rapid advances in neuroscience continue to feed the growth of neuroethics, which is taking an increasingly prominent place in the larger field of bioethics. In 2007, the *American Journal of Bioethics* began publishing twelve issues instead of six, in part to devote a full three issues per year to neuroethics. These special issues, called *AJOB Neuroscience*, are now the official journal of the Neuroethics Society.

Four main developments have stirred discussion and debate in neuroethics this past year: commercialization of lie detection, proposals to use deep brain stimulation for treating depression, advances in the genetic understanding of addiction, and improvements in brain imaging for diagnostic purposes.

Commercialization of Lie Detection

In recent years, advances in the ability to use functional magnetic resonance imaging (fMRI) to map activity in different brain regions fueled research into using the technology for detecting lies. And though the research is still preliminary and the results problematic, two companies have rushed to develop fMRI-based lie-detection products and services: Cephos Corporation and No Lie MRI. The companies say potential uses include crime investigations, parole and child-custody hearings, counterintelligence, and insurance and government security interrogations.

In 2007, the *American Journal of Law and Medicine* published a paper, coauthored by Henry Greely of Stanford and Judy Illes, now of the University of British Columbia, that analyzed existing research on fMRI-based lie detection and made an urgent call for regulation.[1]

Judy Illes has called for regulating lie detection that is based on functional magnetic resonance imaging, in a paper she coauthored with Henry Greely. Studies of the technology have not proved it reliable, the authors say.

The authors argue that while the technology is promising, the existing studies do not prove it to be reliable with any accuracy in the real world, particularly given the artificial and trivial nature of the lies tested in these experiments.

What's more, none of these small-scale studies have been replicated by outside investigators, nor did the studies look at the possibility of subjects' using countermeasures to outwit the lie detectors. The authors' proposed regulatory scheme, modeled after the way the FDA controls the use of drugs, would require marketers of lie-detection technology to prove that it is accurate and effective based on large-scale trials. Under this system, marketing the technology without regulatory approval would be illegal.

Illes also coauthored (with Margaret Eaton of Stanford) a commentary in the April 2007 *Nature Biotechnology* discussing some of the ethical, social, and policy issues associated with the commercialization of cognitive neurotechnology in general.[2] These concerns include accuracy, brain privacy and confidentiality, and potential conflicts of interest for the people bringing these technologies to market.

One danger of an unregulated lie-detection industry is the exploitation of the most vulnerable members of the population, such as those suffering from neurologic or psychiatric disorders. Yet our society seems so eager for lie-detection devices that many people are quick to accept claims that they work, the authors stress.

Deep Brain Stimulation for Severe Depression

Following the success of using deep brain stimulation (DBS) to treat physical symptoms of Parkinson's, and following imaging research that identified a specific brain region involved in depression that might be treated with deep brain stimulation, researchers began clinical trials of this technique in a small number of patients with intractable depression. Findings of remarkable symptomatic relief in many of these surgical patients were published in 2005, but in 2007 the treatment began to receive ethical scrutiny.

Given the relative newness of using deep brain stimulation, even for treating Parkinson's disease, researchers are learning more about unanticipated risks. In June 2007, *Acta Neuropsychiatrica* published a case report documenting how slight adjustments in the electrode contact or voltage in two Parkinson's patients induced life-threatening (suicidal) depression.[3]

Questions of safety are always important, but people tend to accept significant risk in treating debilitating and sometimes deadly diseases such as Parkinson's, researchers say. Depression is far more controversial: some patient advocacy groups believe it is overdiagnosed; some say that even if it is real sufferers should learn to cope with it, and still others cite the existence of many antidepressant drugs.

However, deep brain stimulation is meant for intractable depression, the sort that doesn't respond to drugs. And, lacking effective treatment, patients can be debilitated and are sometimes at risk for suicide. Deep brain stimulation for depression and other clinical uses currently lacks clinical-trial guidelines, and in 2007 a group of leading DBS researchers participated in a consensus development meeting to draft guidelines for experimental use of DBS in patients.

Another ethical concern is informed consent. The impaired cognition and desperation that can accompany severe depression may greatly compromise patients' judgment. Hovering over the whole debate is the specter of electroconvulsive shock therapy, whose therapeutic benefits are not disputed, but whose use remains enormously controversial.

Genetic Underpinnings of Addiction

Several scholarly articles on genes that may underlie addiction were published in 2007. For example, Colin Haile and colleagues published an article titled "Genetics of Dopamine and Its Contribution to Cocaine Addiction" in *Behavior Genetics*.[4] Joel Gelernter and colleagues published "Genomewide Linkage Scan for Nicotine Dependence: Identification of a Chromosome 5 Risk Locus," which appeared in *Biological Psychiatry*.[5]

Evidence suggesting that genes predispose some individuals to addictive behaviors raises ethical questions.

For alcoholism, according to a commentary by Charles O'Brien[6] published in the November 2007 issue of *Addiction*, there is increasing evidence that a variant of the gene for the brain's mu opiate receptor is associated with increased sensitivity to alcohol euphoria, increased risk of alcoholism, increased risk of opiate addiction, and good clinical response to the drug naltrexone for alcoholism in clinical trials.

Evidence suggesting that genes predispose some individuals to addictive behaviors raises ethical questions. One set of questions revolves around testing. If certain genes contribute to addiction but don't determine it with certainty, should we test for them at all? How much predictive power, or value for selecting a treatment, must the genes have before we do decide to test for them? How early should testing begin? Learning that a child is prone to nicotine addiction, for example, might enable parents to take necessary precautions, such as extra education and protection from cigarette ads—or this knowledge might lead to overparenting and unnecessary parental anxiety. Knowing about one's own propensity toward addiction also could become a self-fulfilling prophecy. Additionally, knowledge of predisposing genes, once addiction is diagnosed, would be valuable in selecting the most appropriate treatment.

Counseling raises additional questions: What should a doctor say to a parent whose child has genes that make the child more likely to become a smoker, alcoholic, or heroin addict? The question becomes even thornier if genetic information is available in utero; some parents might reconsider whether they want the pregnancy.

Advance knowledge of propensity toward addiction also raises questions of whether anti-addictive drugs (such as naltrexone) should be given prophylactically, before addiction actually develops. Given the high costs of treating addiction, prospective employers and insurance companies might have a strong vested interest in testing—and could discriminate against carriers of the genes. (Laws currently do prevent unauthorized disclosure of genetic information to insurers and employers.)

Social stigma is another consideration, just as for any genetic abnormality. Mere carriers may have a harder time finding marriage and reproductive partners, and parents may feel guilty for passing on bad genes, even if the child shows no sign of actual addiction. Discussion around these questions is bound to heat up as we learn more about the genetic risk factors for addiction.

Brain Imaging for Diagnostic Purposes

While the use of brain imaging for diagnosing most psychiatric disorders is still a distant prospect, there were strides in 2007 in the experimental use of specific imaging compunds that may identify people with early Alzheimer's and other forms of dementia. In August

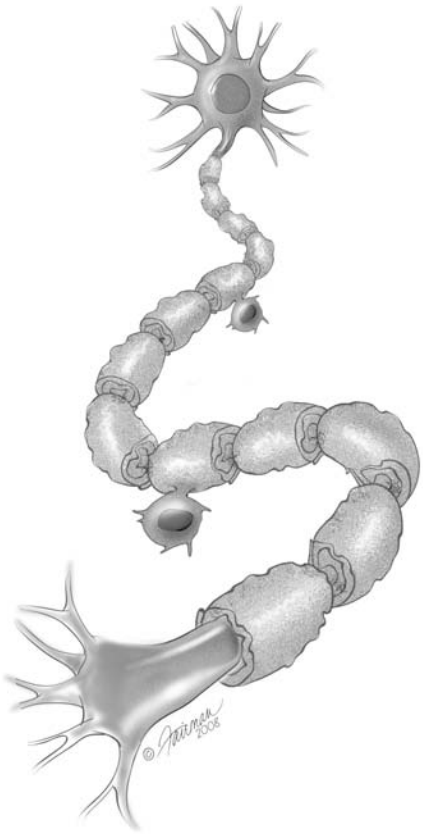
2007, Agneta Nordberg published a review article in *Current Opinion in Neurology*[7] discussing a new amyloid imaging technique using positron emission tomography that shows clear differences between the brains of Alzheimer's patients and healthy controls. This study suggests that early diagnosis of Alzheimer's disease may be possible. Similarly, a case study published in the March 2007 issue of the *Archives of Neurology*[8] reported successful use of the imaging agent Pittsburgh Compound B to spot mild cognitive impairment.

Studies such as these give hope that imaging will help provide more precision for diagnosing anxiety disorders and autism spectrum disorders, once the biological bases of these disorders are better understood. But the hottest area in the search for better diagnosis is with limited states of consciousness, especially in accurately differentiating people who are in a permanent vegetative state from those who are in a minimally conscious state.

While no major technical strides were made in this area in 2007, the ethical framework continued to develop. In June, Judy Illes and Joseph Fins led a well-attended workshop at Stanford University, "Ethics, Neuroimaging, and Limited States of Consciousness," at which scholars discussed these issues. They reached agreement on several aspects of them, including research and clinical goals for carrying out neuroimaging studies of patients in limited states of consciousness, concerns about obtaining informed consent or authorization for such studies, and experimental protocols such as ethically coherent approaches to selecting candidates and designing tests. A special issue of *American Journal of Bioethics Neuroscience* dedicated to this topic is forthcoming.

But even as neuroethicists reach consensus on these questions, and although imaging will undoubtedly continue to improve, researchers and clinicians continue to debate the much trickier questions of how to interpret the brain images and what their prognostic value is in patients with disorders of consciousness. In an April article in *Neurology*, Joseph Fins, Nicholas Schiff, and Kathleen Foley recommended trying to define the epidemiology of the minimally conscious state, clarify mechanisms of recovery, and identify clinically useful diagnostic and prognostic markers to aid decision making at the bedside.[9]

NEUROIMMUNOLOGY



The immune system employs its large and varied arsenal of interdependent cells and their molecules to protect us from a constant onslaught of disease-causing organisms. If improperly targeted or regulated, however, the cells and molecules of the immune system may themselves cause disease.

Although it is not clear why, the immune system appears to be the aggressor in the neurological disease multiple sclerosis. Immune-mediated damage to the insulating coating of nerve cells' axons in the brain and spinal cord interferes with transmission of nerve impulses from one cell to another. Multiple sclerosis can cause a variety of symptoms, ranging from vision disturbances to difficulty walking, and it often follows an up-and-down course in which symptoms periodically worsen.

Both genes and the environment affect susceptibility to multiple sclerosis, but it is likely that many different genes and many different environmental influences interact in the development and progression of disease. Research in 2007 provided new evidence of contributions by genetic and environmental factors that work through the immune system.

Converging on the IL-7 Receptor

In 1972, the genetics involved in multiple sclerosis risk were first linked to a group of immune system genes called HLA. Since then there has been relatively little progress in identifying additional specific genetic risk factors. But the publication of the sequence of the human genome (the complete set of DNA instructions in each human cell) in 2001 has allowed for huge advances in genetic analyses. Using new laboratory techniques and powerful computers, researchers can now analyze previously inconceivable amounts of data, looking for the elusive needle in the genomic haystack.

Of the 3 billion base pairs in the human genome, most of the variation is limited to 250,000 to 500,000 segments of DNA. Simultaneous scanning of these many segments is possible with DNA microarrays, or "gene chips." Genome-wide scans have revealed genes associated with breast cancer, heart disease, and diabetes.[1] These scans require large sample numbers to reveal statistically significant associations when multiple genetic factors each have a small effect. (For more on "genome-wide association," see also Psychiatric, Behavioral, and Addictive Disorders, page 63.)

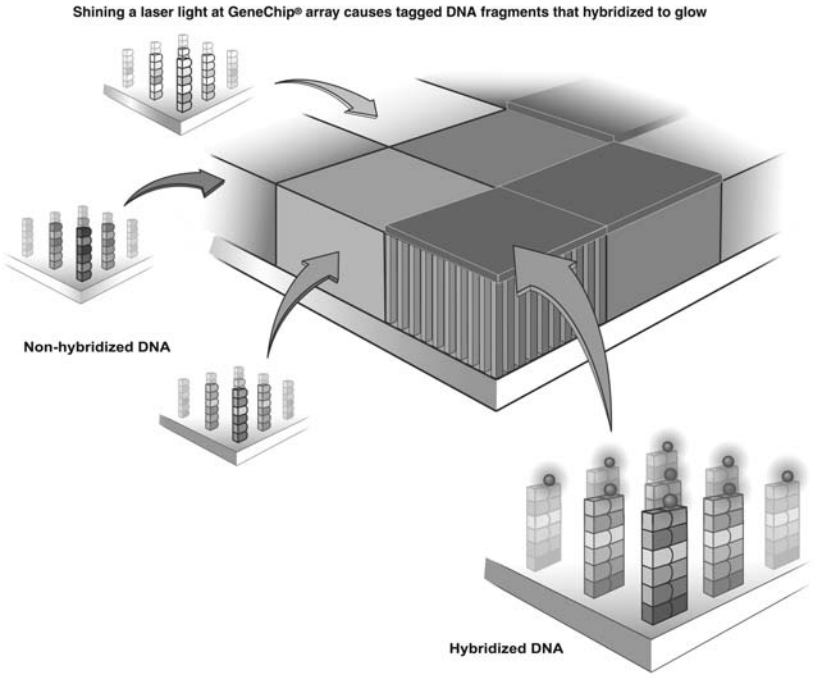
A DNA microarray, or "gene chip," has helped reveal genetic risk factors for multiple sclerosis.

The results of a genome-wide scan for genes that confer risk for multiple sclerosis were published in the August 30 issue of the *New England Journal of Medicine*.[2] An international consortium of investigators used gene chip technology to examine hundreds of thousands of individual genetic changes in a total of more than 12,000 samples. Without any preconceived ideas of what they would find, the investigators confirmed the link between the HLA region and the disease and teased out two other markers, one in the gene for the interleukin-2 (IL-2) receptor and one for the interleukin-7 (IL-7) receptor. Interleukins are immune system proteins through which cells communicate and affect the function of other cells.

These receptors are important for cell-to-cell signaling in the immune system. Like the proteins associated with the HLA gene, the IL-2 and IL-7 receptors are important regulators of the immune system, so it makes sense that the genes that produce these two interleukin receptors might play a role in multiple sclerosis. However, no attempt was made in this study to show anything beyond a statistical association.

Often, genetic studies will turn up several possible genetic risk factors for a particular disease, none of them very strong. Subsequent efforts to confirm such risk factors often fail. Now, by combining several different experimental approaches in what Michael Hauser of the Center for Human Genetics at Duke University dubbed "genomic convergence," scientists can home in on the most promising gene candidates.

A stronger case for a genetic marker can emerge from combining results of studies associating genes with disease within families,



Hybridized DNA fragments glow when a laser light is shined on a microarray, which contains many millions of fragments.

analyzing how genes are inherited together and examining which genes are active in affected tissues. This approach has been used to study the genetics of several complex neurological diseases, including Parkinson's disease and Alzheimer's disease, as well as multiple sclerosis.

As part of a genomic convergence approach to the last, two studies appearing in the September 2007 issue of *Nature Genetics* used targeted searches to look at candidate genes, those that had shown promise in previous functional and genetic studies.[3, 4] Like the genomic scan, the *Nature Genetics* studies also implicated the IL-7 receptor. In fact, they identified the same single-base variation (single-nucleotide polymorphism, or SNP) in the gene that produces the IL-7 receptor.

This particular genetic variation was predicted to make it less likely that the receptor will be bound to the cell membrane, where it can perform its signaling function, and more likely to be present in soluble form, where it can bind up IL-7 and keep it from interacting with cells. Indeed, this was the case, both in the laboratory and in

people with multiple sclerosis. This change would theoretically reduce the effect of IL-7 in the body. In addition, expression of genes for both IL-7 and the IL-7 receptor were altered in the cerebrospinal fluid of people with the disease.

Evidence continues to accumulate that IL-7 and its receptor play an important role in the disease process, though it is not clear how. The increase in disease risk attributed to the IL-7 receptor gene is small, but the IL-7 receptor is getting harder and harder to ignore. Further study of the IL-7 receptor may reveal its role in multiple sclerosis and provide new approaches to treatment.[5]

An IL-7-based pathway in the disease process would be but one of many different disease-promoting mechanisms. Analysis of this and other genetic markers may eventually make it possible to pinpoint what occurs in individual patients, improve diagnostic procedures, and customize patients' treatment plans.

The Sun Sheds Light on Multiple Sclerosis

The risk for developing multiple sclerosis is strongly associated with latitude; living farther from the equator increases the risk. Even people of shared ancestry may differ in susceptibility if they live at different latitudes, especially when they are young. Recent research points to the sun as the reason for this effect.

A study published in *Neurology* examined the effect of childhood sun exposure in pairs of identical twins in North America.[6] The study, led by Thomas Mack of the Keck School of Medicine at the University of Southern California, showed that, within pairs of twins, the one who spent more time outdoors as a child (going to the beach, or playing team sports, for example) had a lower risk of multiple sclerosis. By studying genetically identical twins, the investigators were able to demonstrate the association of environmental factors without the confounding effects of genetic differences.

Another study, conducted in Norway and published in the *Journal of Neurology*, showed that childhood sun exposure reduced risk of multiple sclerosis.[7] The study also showed that a diet rich in fish reduced risk. The authors, led by Margitta Kampman, suggested that the high vitamin D content of fish might be responsible for its protective effect.

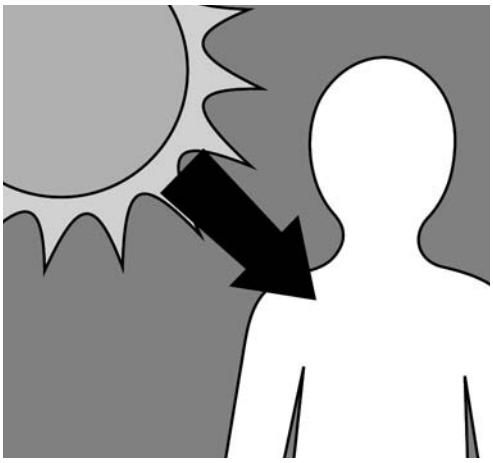
Evidence has indicated a direct effect of vitamin D on the brain. Studies have demonstrated that vitamin D reduces stroke risk in

animal models. The protective effect of sun exposure could come from a direct effect of exposure to ultraviolet radiation or, indirectly, through the production of vitamin D. We obtain some vitamin D from food, but the majority is produced by the skin through exposure to the sun, which is why vitamin D is sometimes called the sunshine vitamin. In winter, when the days are shorter and the sun is lower in the sky, vitamin D deficiencies are common. In fact, people living in latitudes even with or north of Boston obtain no vitamin D at all from the sun between November and February.

Vitamin D is known to be important for maintaining bone density. Perhaps less well known are the regulatory effects of vitamin D on the immune system. Receptors for vitamin D are present on cells of the immune system, and vitamin D deficiency has been associated with autoimmune or inflammatory diseases, including asthma, rheumatoid arthritis, inflammatory bowel disease, and diabetes. Scientists also are exploring the protective role of vitamin D in mouse models of multiple sclerosis.

Several recent population studies have shown that vitamin D levels in the blood correlate inversely with the risk of being diagnosed with multiple sclerosis. A study conducted in Tasmania, Australia, showed that people with the disease had lower blood levels of vitamin D.[8] A study of U.S. military personnel, published December 20, 2006, in the *Journal of the American Medical Association*, measured vitamin D levels over time and found that decreased levels preceded onset of multiple sclerosis symptoms.

This finding supports the interpretation that vitamin D deficiency is a contributing factor to multiple sclerosis, rather than a result of



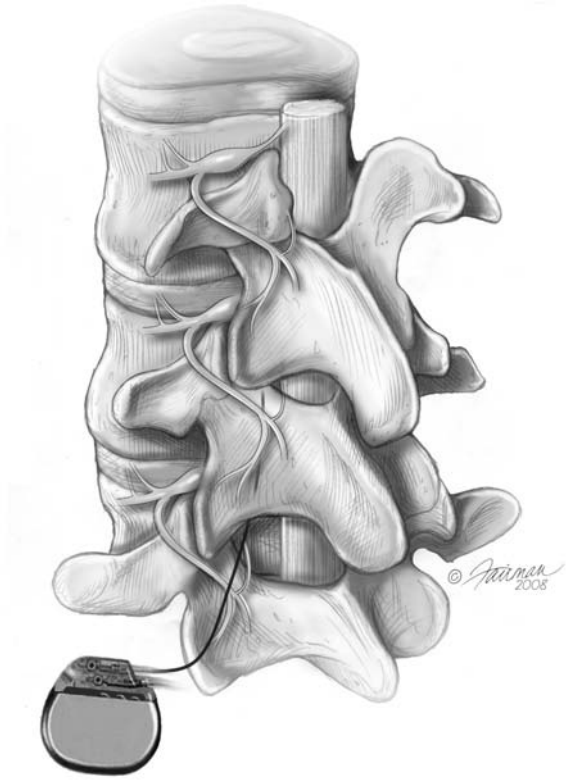
Research in 2007 indicates that vitamin D, produced in the skin through exposure to the sun, may reduce the risk of multiple sclerosis.

reduced sun exposure due to disability.[9] Yet another study, this one from Finland and published in the *Journal of Neurology, Neurosurgery, and Psychiatry* showed that decreased levels of vitamin D in the blood were associated with worsening of symptoms.[10]

Because of its potential effects on susceptibility to multiple sclerosis and other diseases, investigators are taking a new look at recommendations for dietary intake of vitamin D. Currently, the Institute of Medicine of the National Academy of Sciences considers 200 International Units (IU), or 5 micrograms, of vitamin D per day to be adequate for most people aged 50 and under. In September 2007, the Canadian Paediatric Society issued a statement recommending that pregnant and nursing women consider vitamin D supplementation up to 2,000 IU per day.[11]

The group also recommended that babies that are exclusively breastfed get 400 IU of vitamin D and that babies living above 50 degrees latitude (from about as far north as Edmonton, Alberta) receive 800 IU in the winter months. Animal studies suggest that vitamin D can be used to both prevent and treat multiple sclerosis, but more research is needed before these findings can be applied to humans.

PAIN



Pain is the number one reason people seek medical care in the United States. Yet physicians continue to struggle to find effective means of treating and managing both chronic and acute pain.

Pain researchers took several approaches in 2007. Some sought ways to reduce addiction to powerful opioid drugs, which are often the most effective means of providing pain relief. Others identified a crucial pain-signaling pathway that opens new avenues of treatment for patients suffering from significant "phantom" pain following a spinal cord injury. Still others found a more effective treatment for chronic neuropathic pain, offering hope to millions of people who suffer from disabling back pain.

Chronic Pain and Opioid Addiction

For several thousand years, opium has been used to relieve pain and suffering, and many drugs derived from opium, called opioid drugs, are used today for both legitimate and illegitimate purposes. The tendency of these drugs to cause addiction because of their powerful euphoric effect has created a conflict for physicians, who must balance the patient's need for pain relief against the risk of causing dependency.

Although chronic pain diminishes the analgesic effect of many opioid drugs, researchers at Wake Forest University School of Medicine have found that it also weakens an individual's tendency to become addicted to some of these drugs, including morphine, hydromorphone, and fentanyl. The findings, which appeared in the February 27, 2007, issue of *Anesthesiology*, suggest that if chronic pain is not treated adequately with appropriate drugs, patients eventually will stop taking prescribed drugs and seek alternatives, including heroin and methadone, that are more effective at treating chronic pain but that have the feared addictive consequences.[1]

The Wake Forest researchers implanted catheters in rats, half of which had their spinal nerves ligated, or twisted, and then trained them to self-administer clonidine and adenosine, two opioid drugs that effectively reverse hypersensitivity to pain. The researchers found that neither drug had any effect on heroin-seeking behavior in normal rats, because, they say, sites in the brain and not the spinal cord mediate the abuse potential of heroin in a normal animal.

In rats with chronic pain, however, the researchers found that administering clonidine into the spine drastically reduced heroin-seeking behaviors. The administration of adenosine at the spinal level did not affect heroin-seeking in the injured rats, even though this drug is known to alleviate hypersensitivity to pain after nerve injury. These findings suggest, at least in the animal model, that both clonidine and adenosine given together can produce pain relief without producing the urge to use heroin.

A subgroup of chronic pain patients is prone to addictive drug-seeking behavior.

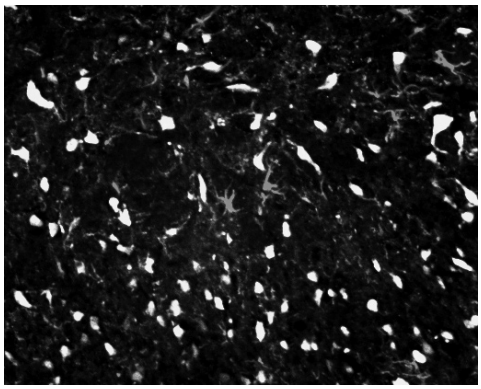
Another study revealed that a subgroup of chronic pain patients is prone to addictive drug-seeking behavior. Researchers at Massachusetts General Hospital examined several studies to determine how opioid addiction relates to chronic pain relief. The researchers reported in the journal *Pain* in June that early assumptions that addiction would be rare among patients treated for chronic pain were incorrect.[2] Rather, drug-seeking and other negative behaviors do occur in a small group of chronic pain patients. How addiction starts, however, is different for this subgroup. Specifically, in this subgroup, the transition to addiction is subtler and more difficult to identify.

Although physicians are armed with a wealth of information that can help prevent opioid addiction when treating patients with chronic pain, the researchers say better tools are needed to help determine who among these patients is likely to become addicted. Physicians, they add, can then develop structured treatment regimens with support from addiction specialists, which may require using alternatives to opioid drugs.

Pain Signal Targeting

Nearly 80 percent of people who suffer a spinal cord injury develop clinically significant pain, describing it as burning, aching, shooting, or stabbing. In addition, many patients who have lost feeling in some parts of their bodies suffer from phantom pain in which they "feel" the body below the spinal cord lesion and experience pain in these areas of total sensory loss.

A dysfunction of the nervous system causes the abnormal pain that



Microglial cells, seen here as bright spots among darker neurons in the lumbar dorsal horn, are part of what cause chronic pain after a spinal cord injury.

often develops following spinal cord injury, say scientists at the Yale University Center for Neuroscience and Regeneration Research. The researchers reported in the February 28, 2007, issue of the *Journal of Neuroscience* that they had demonstrated for the first time a direct signaling pathway in the injured spinal cord between neurons and microglia, immune cells that reside in the central nervous system and mount an inflammatory response to protect the nervous system, but at times may actually damage it.[3]

Using adult rats that underwent spinal cord contusion injury, the researchers found that a molecule called prostaglandin E_2 (PGE_2) is central in microglia-mediated chronic pain. This molecule is released by activated microglia and contributes to the sensitization of spinal neurons after injury.

Targeting this microglia-neuron signaling mechanism, the Yale researchers say, may lead to successful pain management following spinal cord injury. The researchers are examining compounds that block the signaling pathway at several sites in the spinal cord. The prototype compound is minocycline, an antibiotic approved by the Food and Drug Administration to treat a number of infections, which is also in clinical trials to test its effectiveness in currently "off-label" uses to treat several neurological disorders, such as Huntington's disease, amyotrophic lateral sclerosis, and multiple sclerosis.

The Yale team is using a type of imaging called positron emission tomography to attempt to verify evidence that a similar, if not identical, pain mechanism exists in both humans and mice. If so, they will test the effectiveness of minocycline in patients with spinal cord injury in shutting down the PGE_2 pain signaling mechanism.

Effective Back Pain Relief with Neurostimulation

Back pain is one of the most common medical problems in the United States, affecting about 80 percent of the population at some point in their lives. According to a Duke University study in 2004, back pain—in the form of lower back pain, neck pain, or sciatica—costs the United States nearly $100 billion per year in medical bills, disability payments, and lost productivity. Although conventional therapies and surgery have proved somewhat effective at reducing back pain, researchers have found that neurostimulation, a treatment that employs an implantable medical device to deliver electrical impulses, is better at relieving chronic neuropathic pain in the back and legs. These electrical impulses are sent to the epidural space in the spinal column in order to keep pain signals from reaching the brain.

In the largest multi-center, randomized, controlled trial of neurostimulation to date, an international consortium of researchers, led by Krishna Kumar of Regina General Hospital in Canada, found that neurostimulation provides better pain relief, quality of life and functional capacity than conventional treatments, such as pain drugs, pharmaceutical nerve blocks, steroid injections, physical therapy, and chiropractic care.

The study, published in *Pain* in November, found that six months after treatment, nearly half the patients who received neurostimulation along with conventional treatments experienced an improvement in leg pain at least 50 percent greater than the improvement reported by people who received only conventional therapy.[4] Each of the patients had undergone at least one back surgery for a herniated disk but continued to experience moderate to severe pain in one or both legs and in the back at least six months after their surgery.

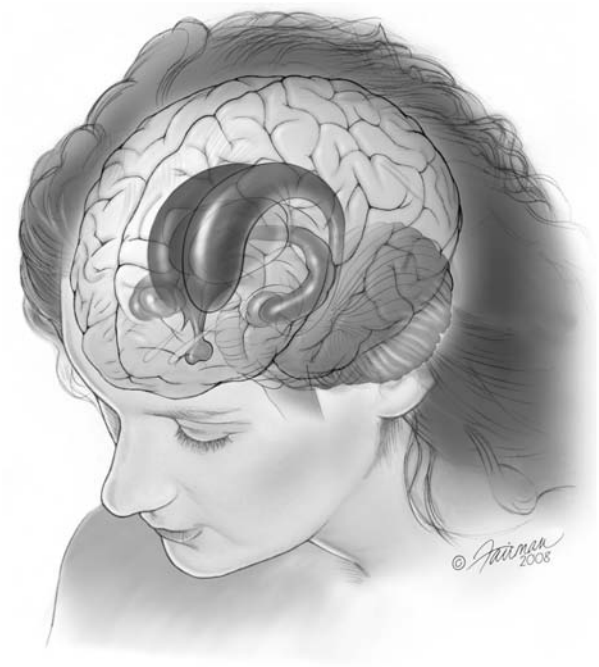
Because disabling neuropathic pain is difficult to treat, the researchers say neurostimulation should be added to the list of treatments routinely offered to patients who suffer chronic back pain.

On the West Coast, physicians at Coast Pain Management in California reported in the July *Neuromodulation* that a specific type of neurostimulation called peripheral nerve field stimulation is a safe and effective alternative for patients with chronic low back pain.[5] The physician-scientists examined the effectiveness of this treatment in six patients with chronic low back pain with whom conventional therapies were unsuccessful. In contrast to spinal cord or direct peripheral nerve stimulation, peripheral nerve field stimulation uses leads placed

through the skin and into the area of pain to stimulate the region of the affected nerves. In each of the six patients, they reported, peripheral nerve field stimulation allowed a reduction in pain medication and an increase in activity level, along with higher quality of life.

Peripheral nerve field stimulation has distinct advantages over other forms of neurostimulation, including fewer complications and lower morbidity, according to the researchers, who say that this treatment shows promise as a complement to existing therapies and deserves further study.

PSYCHIATRIC, BEHAVIORAL, AND ADDICTIVE DISORDERS



Mental health research in 2007 focused on gaining further understanding of the origins of certain disorders and on finding effective treatments. Many scientists maintained an emphasis on the underlying role of genetics in psychiatric disorders but moved toward more targeted study of what role genes play in management and treatment. In addition, neurobiological studies have broadened in scope by examining neural circuits, or connections between distinct parts of the brain, instead of individual regions, to understand how interrupted or misplaced signals may affect mental health.

Recent findings in depression research have led to better understanding of neural circuitry problems that may underlie the disorder, as well as potential non-drug treatments to alleviate these problems. Research into bipolar disorder has yielded a probable genetic indicator as well as the disorder's first mouse model for further study. Finally, studies looking at both schizophrenia and alcoholism have identified new prospective drug treatments.

Depression

The hippocampus, integrally related to the system responsible for human emotion—the limbic system—has long been associated with memory and spatial processing. On the heels of findings that the hippocampus projects to brain areas implicated in depression and that antidepressant-stimulated hippocampal neurogenesis is associated with positive behavioral responses to the drugs, this region also has become an area of interest in the study of depression.

In a *Science* report published August 10, Karl Deisseroth and interdisciplinary colleagues at Stanford University identified a neurophysiological circuit connecting the hippocampus, including the dentate gyrus, to depression.[1] This circuit may be of interest for future interventions.

The researchers subjected one group of rats to stressful situations, such as sleep deprivation, hostile lighting, and loud noises, while a control group lived in a relatively stress-free environment. In addition, some of the stressed rats were given antidepressant medication.

After several weeks, both groups of rats were observed after being submerged in water. The stressed rats that were not given anti-depressants swam less vigorously than the non-stressed and

Researcher Karl Deisseroth and colleagues at Stanford University used a high-speed imaging technique called voltage-sensitive dye imaging to link a faulty circuit in the hippocampus to depression in rats.

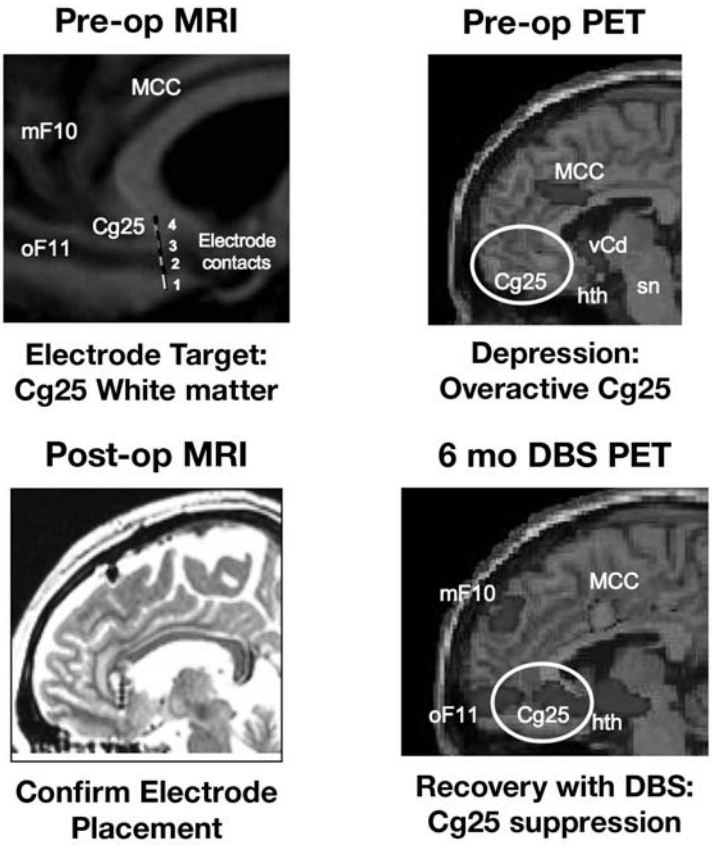
the medicated rats, which the researchers say represents a feeling of hopelessness.

The scientists then used a high-speed imaging technique called voltage-sensitive dye imaging to measure the electrical activity in the rats' hippocampal area, in particular as it projected to the dentate gyrus. They found that the signals successfully conducted across the circuit in the non-stressed and medicated rats but were interrupted in the stressed ones, eventually leading activity in the circuit to die out.

These findings suggest that there may be no single cause for depression but that a single life event, such as a family member's death or a stressful work situation, might cause a problem in the circuit, leading to the pervasive symptoms of depression. The authors also suggest the circuit as a prospective site for treatment therapies.

Other neural circuits in the limbic system have been associated with depression. These circuits often include brain areas such as the prefrontal cortex, amygdale, and subgenual cingulate cortex—areas associated with emotional processing, production of the neurotransmitters involved in sad emotions, and response to antidepressant drugs.

In a September *Nature Neuroscience* review by Kerry J. Ressler and Helen S. Mayberg of Emory University's Department of Psychiatry and Behavioral Sciences, the authors argue that progress made in identifying and understanding the actions of depression-associated neural circuits, and in pinpointing specific areas within these circuits where their dysregulation is associated with behavioral symptoms, now makes the use of promising non-drug therapies feasible.[2] Finding effective alternatives to currently available antidepressant medications is critically important for people with intractable depression who do not respond to these medications.



Earlier imaging studies associated too much activity in area Cg25, part of the subgenual cingulate cortex, with severe depression. Work in 2007 suggests that deep brain stimulation in area Cg25 has an antidepressant effect. These images show a reduction in blood flow to area Cg25 after deep brain stimulation, which involves the stimulation of an implanted electrode.

Foremost among these non-drug approaches is deep brain stimulation (see also Movement Disorders, page 27, and Neuroethics, page 43). Clinical studies of deep brain stimulation for treating intractable depression were based on Mayberg's initial imaging studies, using positron emission tomography, that identified the subgenual cingulate cortex (Cg25) as an area associated with severe depression. Deep brain stimulation alters communication within and among brain circuits in this region via high-frequency stimulation to implanted electrodes.

The treatment was associated with antidepressant effects, a marked reduction in cerebral blood flow to area Cg25, and changes in multiple brain regions implicated in mood regulation and treatment response. Further clinical studies are under way in a larger number

of patients to further establish the treatment's safety and efficacy, to determine how brain circuitry in this region is involved in depression, and to determine how deep brain stimulation effectively intervenes in this circuitry.

Other potential alternatives to antidepressant medications include vagus nerve stimulation, electroconvulsive therapy, and repetitive transcranial magnetic stimulation. While electroconvulsive therapy has long been used to treat intractible depression and has regained acceptance in recent years, deep brain stimulation, vagus nerve stimulation, and transcranial magnetic stimulation all are being tested to determine their ability to interrupt and modify brain circuits that have been linked to depression and emotion regulation.

By using neuroimaging techniques such as positron emission tomography and functional magnetic resonance imaging before and after treatment, scientists are able to see changes in regional activation in the brain, showing the changes to the circuits involved. Improved understanding of the underlying neural circuitry may also make these therapies viable candidates to treat other psychiatric disorders, such as obsessive-compulsive disorder.

Although deep brain stimulation is now an accepted treatment for Parkinson's disease patients who are no longer able to tolerate drug treatment with L-DOPA and shows promise in treating intractable depression, Ressler and Mayberg suggest that more research is needed, not only to better understand the long-term effects to patients but also to define optimal treatment conditions.

Bipolar Disorder

Previous studies have suggested that problems with the regulation of circadian rhythms, or the body's internal clock, may play a pivotal role in bipolar disorder, a psychiatric condition sometimes also referred to as manic depression. In a study published in *Proceedings of the National Academy of Sciences USA*, Colleen McClung and colleagues created the first mutant mouse model of bipolar disorder by disrupting a gene called *clock* (circadian locomotor output cycles kaput) by inducing mutations to proteins that regulate the animal's circadian rhythms.[3]

Clock is believed to produce a protein necessary to regulate the complex feedback loop governing circadian rhythms in the brain. McClung's mutant, *clock*-free mice showed mania-type behaviors that

mimic human bipolar symptoms. Those symptoms included hyperactivity and reduced sleep time as well as heightened response to novel stimuli and stimulants such as cocaine.

The *clock* mutant mouse is the first animal model of mania to be created, offering the potential for greater understanding of how circadian rhythms are neurally and genetically regulated and how dysregulation may lead to bipolar symptoms. Furthermore, the model presents researchers with a new direction in which to develop new and improved treatment options for bipolar patients.

Obsessive-Compulsive Disorder

In the past few years, research into obsessive-compulsive disorder (OCD) has consistently implicated the striatum, the input center of the basal ganglia system. Malfunctions in this system have been implicated in dysfunction of motor control, learning, and reward processing.

Guoping Feng and colleagues studied the role of a gene that is prevalent in the striatum. In a paper published in *Nature*, Feng's team used gene knockout techniques to remove from mice the *sapap3* gene, which is critical for the effective synaptic communication of neurons in the brain that use the neurotransmitter glutamate.[4]

Previous studies and treatments focused on the neurotransmitter serotonin, so this result, implicating glutamate, may inspire work on new drug therapies that target glutamate neurotransmission.

The *sapap3* mutant mice showed several OCD-like symptoms, including increased anxiety and excessive personal grooming to the point of hair loss. However, when the mice were treated with fluoxetine (Prozac), a drug commonly used to treat OCD, or when the *sapap3* gene was directly reinserted into the striatum of the mutated mice, the symptoms abated.

These findings provide new insight into both the underlying neurobiological causes of obsessive-compulsive disorder and avenues for future treatment. Previous studies and treatments focused on the neurotransmitter serotonin, so this result, implicating glutamate, may inspire work on new drug therapies that target glutamate neurotransmission.

Schizophrenia

In 2005 and 2006, a group of independent studies showed that atypical, or second-generation, anti-psychotic medications were less effective than older drugs that often cause more side effects. In one study, led by Jeffrey Lieberman and published in 2005 in the *New England Journal of Medicine*, the exception was olanzapine, an atypical drug with which patients discontinued use at a lower rate than with its peers.[5] However, patients experienced persistent weight gain and other metabolic side effects. The results of these studies caused widespread concern among psychiatrists and researchers about treatment options for schizophrenic patients.

Another group of researchers, led by Sandeep Patil of Lilly Research Laboratories, tested a new drug called LY2140023, which moderates the neurotransmitter glutamate in the brain. In a paper in the September *Nature Medicine*, the researchers compared the new drug with olanzapine and a placebo for four weeks in 200 patients with schizophrenia.[6]

The group found that more than 25 percent of patients who took LY2140023 responded positively to treatment, without negative side effects. The results suggest that drugs that help the brain adapt to disrupted glutamate pathways may be a safe and useful treatment option in the future for those suffering from schizophrenia.

Alcoholism

Drugs have been used with mixed success in the treatment of alcoholism. A study by Lara Ray and Kent Hutchison that appeared in September in the *Archives of General Psychiatry* suggests that naltrexone, an opioid receptor antagonist and one of the drugs prescribed to combat alcoholism, is more successful in the treatment of individuals with a certain genotype than others.[7]

Ray and Hutchison found that people addicted to alcohol who had a certain type of a gene called *OPRM1* not only reported greater feelings of intoxication after drinking but also had a reduced response to alcohol after taking naltrexone. These results provide an avenue for further study not only of genetic indicators in alcoholism but also of how those indicators may interact with treatment.

Future Directions in Study and Treatment

The completion of the International HapMap Project, a catalog of common human genetic variants, in 2005 has provided mental health researchers with a new opportunity to undertake whole-genome studies to identify genetic factors underlying complex psychiatric disorders. "Genome-wide association" studies in heart disease, diabetes, and certain cancers have yielded extensive new avenues for the discovery of disease development and treatment, and scientists are hopeful that comparable studies examining schizophrenia, bipolar disorder, and obsessive-compulsive disorder will yield similar success.

Thomas R. Insel, director of the National Institute of Mental Health, and Thomas Lehner of the institute's Division of Neuroscience and Basic Behavioral Science argue in a May editorial in *Biological Psychiatry* that the potential for genome-wide association is high but that researchers need to consider the requirements to successfully carry out these analyses.[8] Large sample sizes with well-defined characteristics are a must, which may be difficult for smaller research laboratories with a small pool of patients. Also, disorders with broad or contentious diagnostic criteria may present difficulties in narrowing down the genetic factors involved.

To combat these issues, the authors advocate the sharing of genomic databases. One such database is the NIMH's bipolar disorder phenome database. Researchers at the institute compiled a database of validated variables for more than 5,000 people with bipolar disorder.[9]

The database is available to laboratories and research centers to identify genetic indicators and effects. As more such databases are assembled and made available for public use, a more sophisticated understanding of the role of genes in psychiatric disorders, as well as opportunities for new and more effective treatments, may be possible.

SENSE AND BODY FUNCTION

In 2007, scientists continued to explore the ways in which the brain processes and responds to perceived stimulation. Researchers at Harvard University investigated the mechanism by which we feel sick and took the first steps toward reducing those sensations for patients with certain conditions. Researchers at both Duke and Johns Hopkins universities made progress in the complicated investigation of sound perception, studying music and speech, respectively.

The Fever Response

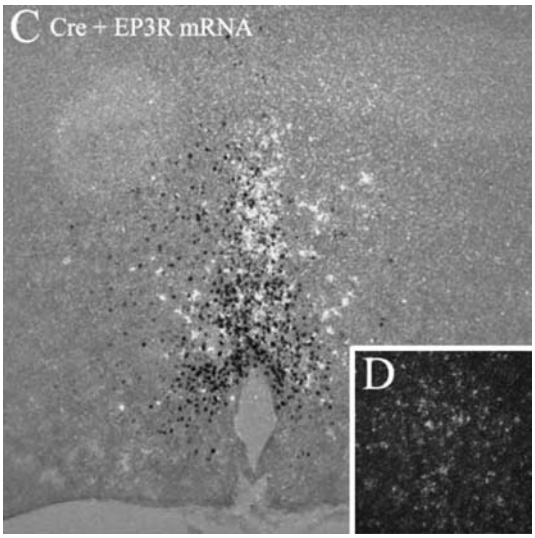
A person who feels as though he or she is getting sick typically experiences a familiar set of symptoms: body aches, fatigue, poor appetite, and the chills and hot flashes associated with a fever. The body develops a fever in response to several situations perceived as threats. Bacterial infections are the most common fever-producing events, but some viral infections, along with noninfectious diseases involving the immune system, such as rheumatoid arthritis and Crohn's disease, will also prompt the body to elevate its temperature above 98.6 degrees Fahrenheit.

Although running a fever is an unpleasant experience, fevers aid the body in its fight against infection. White blood cells, which are part of the body's immune system, become more active when the body's temperature elevates, mounting a stronger defense against the invading organisms.[1] Infectious agents also have a more difficult time surviving and flourishing in a system that is getting hotter. Until recently, however, scientists did not fully understand the mechanism by which fevers are produced.

Scientists knew that a fever occurs when prostaglandin E_2 (PGE_2), a hormone made by blood vessels on the edge of the brain, is released into the blood, crosses into the brain, and binds to EP_3 prostaglandin receptors (EP_3Rs). These receptors are located in the part of the hypothalamus called the median preoptic nucleus as well as in other parts of the central nervous system.

The question that Clifford B. Saper and his research team at Harvard sought to answer in 2007 was this: which receptors respond to the PGE_2 hormone by triggering the body to run a fever?

Saper's team investigated receptor response via a viral vector—a benign virus modified to deliver specific genetic material—called adeno-associated virus. In this case, adeno-associated virus selectively



Researchers were able to prevent the development of fevers in mice by blocking EP_3 prostaglandin receptors (stained white) above the third ventricle, a normal opening in the brain. The dark cells have been affected by the injection of a gene that blocks EP_3 receptors. The inset shows a higher magnification of this process.

"chopped out" the EP_3 gene, thereby preventing any PGE_2 hormone from binding at that site. The team incapacitated receptors in the brains of mice, working with one specific, tiny area at a time, and then tested the animals' fever response.

When the EP_3R located in the median preoptic nucleus were incapacitated—when the EP_3 genes there were "chopped out"—the mice did not develop fevers in response to infection.[2]

Saper's team suspects that the PGE_2 hormone and its EP_3R are responsible for the range of familiar symptoms one feels when one feels sick, because drugs such as aspirin and ibuprofen, which block the synthesis of prostaglandins, reduce both fever and pain. They decided to begin by investigating the fever response for two reasons. First, it is relatively easy to measure body temperature (easier than measuring aches or fatigue). Second, the research on fever was further along than research on the other responses to infection. In 2008, Saper and his colleagues will again use mice to explore the role that the PGE_2 hormone and its EP_3R_S play in generating the pain response to illness.

If the mechanism by which the body experiences pain when it is sick can be deciphered as exactly as the mechanism by which it runs a fever, pain could then be controlled by managing the PGE_2 hormone and its receptors. This progression would potentially provide clinicians with an alternative to narcotics and other pain management remedies when they are treating the discomfort of patients with chronic or terminal diseases—situations in which the pain response is

no longer prophylactic and adaptive. Ideally, physicians could simply "dial down" the pain response in these patients to increase their quality of life.

The Universal Human Appreciation of Music

The human ear can hear a wide variety of tones, but musicologists who study music across different cultures have determined that people use approximately the same small subset of tones called scales in the creation of music. Dale Purves and his research team at Duke wondered why, and they hypothesized that it had something to do with the tones present in human speech. In 2007, these researchers set out to decode the connection between human speech and the musical tones that all humans find agreeable.

Initially, the team thought the preferred intervals in music mimicked the rise and fall of pitch when humans speak. They expected to be able to map common voice modulation over commonly used scales, but the intervals were not the same. The team then turned to what are called formants.

When an instrument produces a note, that note can be represented as a spectrum. Formants are the most important frequency components represented when an instrument, including the human voice box, generates a note. When a person speaks a vowel sound, it is those strongest pitches, or formants, that make the sound distinguishable from other vowel sounds.

Purves and his colleagues statistically analyzed spectra created by music and spoken vowels (the spectra were represented visually) and discovered that 68 percent of the time, the same intervals that create the music deemed pleasing by humans across time and geography were also emphasized when people spoke vowel sounds.[3] The emphasized harmonics in human speech—the frequencies that harmonize and form what we recognize as a person speaking a vowel sound—are often the same as our chromatic musical intervals. In other words, the tones of music are actually embedded in our speech.

The principles of evolutionary weeding suggest that humans' aesthetic taste is rooted in something practical. This discovery suggests that the harmonies the brain finds pleasing identify aspects of our environment that bear important information, or did at one time. Paying attention to another person speaking used to spell the difference between life and death (it still can); those who found speech

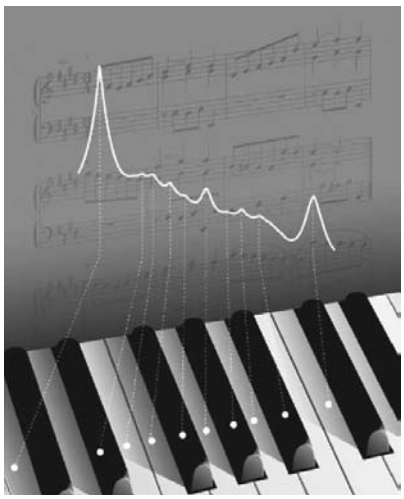
most pleasant listened, reaped its lifesaving benefits, and went on to reproduce. The descendants of those early humans eventually used those same lovely intervals to create music, this theory suggests.

Exploring music in this way has piqued Purves's interest, and he plans to investigate the link between music and emotions next. Humans interpret music played in a major scale as bright and hopeful, while a tune in a minor scale seems melancholic. Purves speculates that changes in the larynx, which occur in response to activity in the nervous system, cause formant changes when we speak that reflect these major and minor scales. According to this theory, a happy person's nervous system cues the larynx to produce major-scale formants; a sad person's nervous system results in minor-scale formants.

The Complex Perception of Spoken Language

In the 1970s, Murray Sachs and Eric D. Young of Johns Hopkins University discovered the mechanism whereby the brain codes, and therefore understands, speech. They discovered that hair cells in the ear vibrate in response to sound, and that this vibration is translated into an electrical signal—a nerve spike—that the auditory nerve conducts to other parts of the brain.

In the 1980s, they shed light on how the brain represents the variety of information that is carried in through the ears. Each of the 30,000 auditory nerve fibers represents a very small number of specific frequencies. The dominant frequencies, or formants—the same patterns examined by Purves's team—are then extracted in the



The intervals between notes in the chromatic musical scale (the marked piano keys) correspond to key human speech tones (the crests of the white line). These peaks allow us to recognize vowel sounds and may help explain why humans appreciate certain tones as musical.

cochlear nucleus, which interprets auditory nerve fibers' responses to frequency.

Xiaoqin Wang, who has since joined the research group, is interested in how the brain processes speech-like stimuli in the auditory cortex. He began by using marmoset monkeys to study how animals determine which auditory stimuli are worth their attention. Marmosets were selected for the range of their vocal repertoire; they chirp to convey many kinds of social and practical information. They also continue to chirp in meaningful ways in captivity. Wang and his team played recorded monkey calls forward (as they are normally heard) and then backward, and determined that monkeys and cats process monkey calls differently. The cats' response to the monkey calls did not change based on how the calls were played, but the neurons in the same-species monkeys responded more strongly to the forward, familiar version of the call. Thus it was determined that animals process the sounds of their own species uniquely, and those differences showed up in a part of the brain called the inferior colliculus.

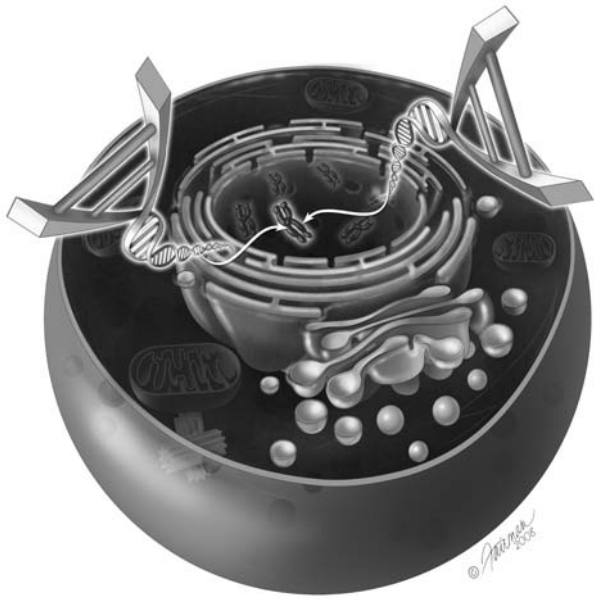
The inferior colliculus, which Young has studied extensively, introduces time as a factor in understanding speech. When we listen to speech, we hear, decipher, and store individual sounds in our short-term memory, and we anticipate the next sounds. When we listen to multiple speakers simultaneously, as in a group discussion, those streams are understood separately and kept distinct. The speed at which the brain can make sense of speech is what allows it to be a practical way for humans to convey information.

Currently, Young is investigating how the auditory system uses short-term memory along with moment-to-moment processing of sound to make sense of language. The next step in his inquiry will be to study the mechanisms by which we are able to anticipate what a person will say next.

Sachs plans to rejoin Young and Wang in the lab in 2008 to begin studying how one marmoset monkey distinguishes the calls of another specific monkey when many, both seen and unseen, are chirping away. This isolation of all the sounds from one source is referred to as forming an auditory object. The researchers are looking for neurons in the inferior colliculus that do this analysis, the same sort of analysis that allows humans to make sense of speech in a crowd or identify the sound of a particular instrument in a band or orchestra.

The group also plans to study the process of perceiving music. Like Purves, Sachs is interested in how sound affects emotions.

STEM CELLS AND NEUROGENESIS



The immature, versatile precursors to human tissue known as stem cells continue to show promise in understanding and treating disease—particularly neurodegenerative diseases, in which crucial populations of brain cells begin to die. In 2007, researchers reported new ways of obtaining stem cells in quantity, without engendering ethical concerns, for use throughout the body, including the brain. Additionally, studies have revealed how stem cells can help to unravel processes of neural degeneration and be used effectively to deliver therapies to dying brain cells.

Stem Cells from Skin Tissue

In 2007, stem cell research took a giant step closer to a long-desired goal: coaxing cells from adult human tissue to behave like embryonic stem cells, thus sidestepping the ethical hurdles posed by the use of embryos. In the November 20 *Cell*, Shinya Yamanaka and colleagues at Kyoto University, Japan, inserted four genes that are active during embryonic development into a modified virus. The virus was then inserted into fibroblasts, which are skin cells taken from adults. These genes then "reprogrammed" the skin cells to produce a line of stem cells that could self-renew and produce as many new cells as embryonic stem cells ordinarily produce.[1] Another team, led by James Thompson of the University of Wisconsin, Madison, used a slightly different combination of genes to similarly reprogram skin cells taken from newborns. Their results appeared online November 19 and in print December 21 in *Science*.[2]

Stem cells produced through this method have the same "pluripotency" of embryonic stem cells, meaning they can develop into any desired type of tissue. Two studies in the July 19 *Nature*, one by Yamanaka and one by Rudolph Jaenisch of the Whitehead Institute, Boston, and colleagues, demonstrated this pluripotency in cell lines produced from mouse skin cells using the same basic technique.[3, 4]

The most immediate use of this technique will be to produce cell lines that contain genes known to produce specific diseases, such as the inherited forms of Alzheimer's or Parkinson's disease. These cell lines can be used to investigate how the gene products produce neurodegeneration and to screen potential therapies. Ultimately this new stem cell technique is expected to usher in a new age of medicine in which many brain diseases can be treated by replacing damaged

nerve cells with a new population of brain cells derived from the patient's own skin cells. But many hurdles remain. For example, use of modified viruses to deliver genes into skin cells may lead to development of tumors. Additionally, the stem cells derived from skin cells are not identical to those produced by embryos, and the differences may prove significant. While these potential problems will need to be successfully addressed, the ability to produce stem cells in quantity without involving fertilized human embryos is a major step forward.

Stem Cells from Non-Viable Embryos

The successful cloning of Dolly the sheep in 1997, by a process known as somatic cell nuclear transfer, raised hopes that the same approach could produce an endless supply of stem cells—either healthy cells from the patient or, for research purposes, cells with a particular genetic disorder. The process, however, involves inserting the desired genetic material into an oocyte, or egg cell. Obtaining egg cells from humans in sufficient numbers poses technical and ethical hurdles.

A study in the June 7 *Nature* shows a way around many of these hurdles. Working with mice, Dieter Egli and colleagues at Harvard University showed that it is possible to introduce stem-cell material into fertilized embryos, or zygotes—something that previous research had failed to accomplish.

In one phase of the experiment the researchers took zygotes with extra chromosomes—which are non-viable and thus cannot develop into living offspring—removed the abnormal chromosomes, and inserted the DNA of the stem cells they wanted to propagate. An estimated 3 to 5 percent of the human zygotes in in vitro fertilization clinics carry such abnormalities and are usually discarded, according to a 2000 report of the American Society for Reproductive Medicine/Society for Assisted Reproductive Technology Registry.[5] The study shows for the first time how these unusable zygotes—numbering in the tens of thousands—could generate a vast supply of stem cells.

This approach would not destroy a potential life, since the embryos' chromosomal abnormalities are incompatible with life. In addition, the genetic material in the resulting stem cells would not be that of the original donors. The technique could provide an ethically acceptable way of generating stem cells in quantity for use in researching many human genetic disorders.[6]

Not All Neural Stem Cells Are Alike

In seeking to harness the therapeutic power of neural stem cells, researchers need a thorough understanding of the factors that control their development. A common assumption is that neural stem cells begin life in a uniform state of potential and can theoretically be nudged onto almost any developmental path.

However, this assumption is based on studies of cultured cells; less is known about how stem cells behave in the brain. A study in the July 20 *Science* shows that a stem cell's fate is restricted depending on its location.[7]

Working with newborn and adult mice, Arturo Alvarez-Buylla of the University of California at San Francisco and colleagues tracked the progeny of small groups of stem cells. Stem cells were selectively, and permanently, labeled with green fluorescent protein. The team followed the fate of stem cells from 15 different locations of a large "germinal" brain region in the adult, where neurons and other brain cells continue to be born after birth.

Mature, green-labeled nerve cells were formed from all sites, but the types of neurons produced differed depending on the site of origin. In addition, the stem cells proved remarkably resistant to a change in environment. Even when removed from the brain and grown in culture, exposed to a variety of growth factors—or when grafted into different sites in the germinal regions of other animals—the stem cells gave rise to neurons and other brain cells, but the neurons produced were once again specific to their original location. The finding suggests that although stem cells are indeed versatile, the types of neurons an individual stem cell can generate may be specified for one part of the brain and not readily able to assume a new identity if transplanted to a different location. This region specificity might restrict the therapeutic usefulness of a given population of stem cells.

Stem Cells Protect Neurons in ALS

Stem cells are usually hailed for their potential to produce future generations of healthy replacements for cells that die in degenerative disease. But they can also be used to deliver therapeutic substances to ailing neurons.

Working with a line of embryonic stem cells, Clive Svendsen of the

Clive Svendsen of the University of Wisconsin, Madison, and colleagues have developed stem cells that secrete a neuron-protecting compound called glial-derived neurotrophic factor, or GDNF. Implants of these cells kept damaged motor neurons alive in rats with early-stage ALS.

University of Wisconsin, Madison, and colleagues engineered stem cells to secrete a compound called glial-derived neurotrophic factor (GDNF), which nourishes and protects neurons. Reporting in the July 31 edition of PLoS One, the online journal of the Public Library of Science, the investigators implanted GDNF-secreting stem cells into the spinal cords of rats with amyotrophic lateral sclerosis (ALS, or Lou Gehrig's disease), which attacks motor neurons.[8]

The transplants took hold and, in rats with early-stage disease, protected virtually all of the injured neurons. The engineered cells also showed a high affinity for damaged neurons, moving directly to the injured areas and pumping out GDNF.

The procedure did not restore communication between motor neurons and muscles or improve the rats' ability to use their limbs; as a treatment for ALS its role would be limited to keeping the neurons alive. However, the approach demonstrates a lesser-known use for stem cells that could be useful in treating a variety of disorders. This approach of using stem cells to travel to sites of damage in the brain is also being investigated for delivering targeted treatment to brain tumors.

Powerful New Tools to Study Disease

Two teams of researchers studying amyotrophic lateral sclerosis have used stem cells to provide a vital clue to this mysterious disease. More than 90 percent of cases are sporadic, meaning that the patient has no family history of the disease. However, a mutated gene that encodes an enzyme called superoxide dismutase-1 (SOD1) has been identified as a cause of the disease in a few people.

How the mutated gene damages motor neurons is not understood. In particular, it is not known if the damaged gene directly affects motor neuron function or if other cells are involved. Recent studies have found that even healthy motor neurons begin to show characteristics of ALS when cultured with non-neuronal cells carrying the mutation.

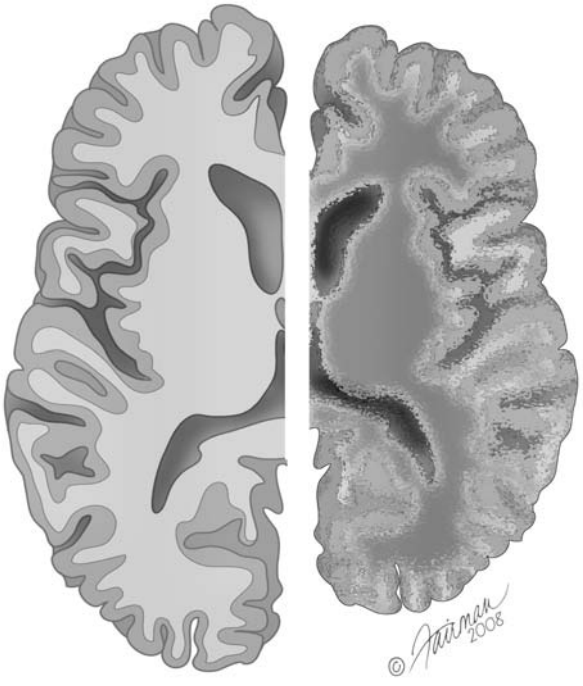
The new studies, both published in the May *Nature Neuroscience*, suggest that the culprit is the star-shaped cells called astrocytes, which play many supportive roles in the brain. Working with motor neurons taken directly from mouse embryos, as well as neurons derived from mouse embryonic stem cells, researchers led by Serge Przedborski at Columbia University found in the first study that motor neurons carrying the human SOD mutation showed some abnormalities, but not neurodegeneration.[9]

However, astrocytes with the mutation triggered motor neuron death, following the same degenerative pathway as occurs in ALS. In addition, the team found that the astrocytes cause damage by releasing a substance that is selectively toxic to motor neurons, in contrast to non-harmful substances released by other types of support cells, such as glia.

In the second study, Kevin Eggan and colleagues at Harvard University and Perugia University used embryonic stem cells from mice to create a model to study the same question.[10] The researchers took stem cells of mice bred to have either the normal human SOD gene or the mutated version, then allowed them to differentiate into motor neurons in large numbers. Cells with the mutation went through the characteristic steps of the disease, leading to the death of motor neurons, which suggests that the stem-cell approach is an effective, long-term research model of ALS. In addition, both the normal and the mutated motor neurons showed signs of neurodegeneration when cultured with SOD-mutant support cells.

Both findings open up new routes to treatment by showing that ALS may result from factors, such as astrocytes, that are not intrinsic to the motor neuron but that affect it. They also show how stem cells can provide a powerful new tool for studying the process by which a disease unfolds—in the case of the latter study, the work even provides a cell-based method for screening potential new drugs.

THINKING AND REMEMBERING



Research in 2007 plowed new ground in understanding and treating neurodegenerative diseases, including Alzheimer's. A growing body of evidence is also leading to new insights into how the brain uses memories of the past to plan for the future.

No treatment has yet been proved to modify the course of Alzheimer's disease, but researchers are drawing close on a number of fronts that, in combination, may advance treatment and maybe even prevention of Alzheimer's disease. A protein called beta-amyloid is one focus, but research continues on other targets as well.

Beta-amyloid and Alzheimer's

Several of the research advances concern beta-amyloid protein plaques and fibrils, which build up in the brains of patients with Alzheimer's disease. Plaques form in spaces between brain cells, and fibrils (tangles) develop within brain cells, but research suggests that neurons are damaged and brain functions are impaired before such structures appear.

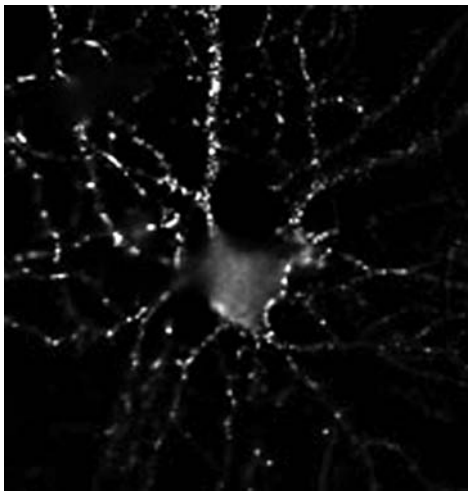
Results of diverse studies using synthetic beta-amyloid peptides, cell culture models, transgenic mice (genetically engineered to contain human DNA), and the human brain all point in one direction: progressive accumulation of beta-amyloid is toxic to cells long before visible plaques and fibrils form. The subunits, or building blocks, of beta-amyloid protein were the subject of much research in 2007.

A team led by Lennart Mucke at the University of California, San Francisco, studied transgenic mice that have large amounts of beta-amyloid subunits in their brains; the animals exhibit many of the symptoms of Alzheimer's, including cognitive deficits.[1]

The researchers found high levels of nonconvulsive seizure activity in the hippocampus and cortex, structures known to be important to memory. In those regions, beta-amyloid subunits cause an increased rate of firing in certain excitatory neuronal circuits. In response, inhibitory circuits remodel themselves. The effect is a reduction in the firing rate of the excitatory circuits.

The team concluded that the cognitive deficits associated with Alzheimer's disease may result from the combination of excessive neuronal firing, caused by beta-amyloid subunits, followed by compensatory remodeling of inhibitory circuits. The remodeling may impair the function of the excitatory circuits.

Mucke suggests that treatments that block beta-amyloid-induced



ADDLs, toxic proteins that build up in the brain and cerebrospinal fluid in Alzheimer's disease, attack the memory-building synapses of a brain cell. Researchers in 2007 studied the effect of ADDLs.

over-excitement of neurons might prevent the activation of inhibitory pathways, their subsequent remodeling, and the cognitive impairments that ensue.

Elsewhere, a Northwestern University team led by William Klein investigated how beta-amyloid-driven subunits called ADDLs affect synapse composition, structure, and abundance.[2] These molecules build up in the brain and the cerebrospinal fluid. They attach to synapses, where they interfere with plasticity, the ability of the synapse to change. Eventually, the synapse degenerates, bringing on the memory loss of early Alzheimer's disease.

Klein and his team investigated dendritic spines, which are outgrowths on the smaller, branching extensions of neurons. In most neurons, dendrites carry impulses toward the nerve cell body.

Using neurons cultured from the hippocampus, Klein and his colleagues found that ADDLs bind to dendritic spines in specific kinds of neurons and cause an increase in the number of certain memory-related receptors. Continued exposure leads to abnormally long, thin dendritic spines and, eventually, to a reduction in the number of spines. As a result, synapses deteriorate. The anti-Alzheimer's drug Namenda blocks both effects, the researchers found.

In a related study, a team led by Bernardo Sabatini at Harvard demonstrated that two- and three-molecule subunits (but not single-molecule subunits) from beta-amyloid-derived proteins brought on progressive loss of synapses in hippocampal cells.[3] The density of spines on dendrites and the number of active synapses in pyramidal neurons declined after exposure to the small, soluble molecules.

Beta-amyloid-specific antibodies reversed the loss of spines, as did a substance that prevented the buildup of the small molecules into larger units. Sabatini concluded that small, soluble subunits of beta-amyloid trigger the loss of synapses.

The exact molecular structure of these soluble, diffusible subunits that merge into visible plaques and fibrils is still being probed. Nevertheless, therapies aimed at preventing the production of the subunits are being developed and tested. The goal of such treatments is to slow or even halt the deterioration of neuronal circuits before Alzheimer's symptoms appear.[4]

Genetic Variants

Beta-amyloid is made from amyloid precursor protein (APP) in several parts of the cell. One important step in beta-amyloid manufacturing occurs during the re-entry and recycling of APP as it moves from the cell surface through a specific pathway inside the cell. A large international team of researchers led by Peter St. George-Hyslop of the University of Toronto reasoned that inherited differences in that pathway might affect both the processing of APP and the risk of developing Alzheimer's.

They reported in *Nature Genetics* that inherited differences in a gene called *SORL1* are associated with late-onset Alzheimer's disease.[5] The variants occur in at least two different clusters of noncoding DNA within the *SORL1* gene. These clusters may regulate how *SORL1* is expressed in brain tissues.

The team found that *SORL1* directs APP into recycling pathways. When there is a shortage of *SORL1*, APP is sorted into compartments where beta-amyloid proteins form. The researchers concluded that inherited or acquired changes in *SORL1* expression or function are one cause of Alzheimer's disease.

Other Targets for Treatment

Beta-amyloid proteins are not the only targets for potential Alzheimer's treatment. Another is a protein called tau.

Tau is abundant in normal neurons. It interacts with the protein tubulin to promote and stabilize microtubules, the hollow, cylinder-shaped structures in a cell that support it and move materials through it.

However, certain abnormal forms of tau can trigger the assembly of the tangles and filaments found in the neurons of Alzheimer's patients. Researchers are attempting to learn whether treatments aimed at tau can block beta-amyloid-induced cognitive impairments.

A team led by Eric Roberson at the Gladstone Institute of Neurological Disease in San Francisco used transgenic mice to probe this question. The mice were engineered to express high levels of amyloid precursor protein. They were tested in a water maze for learning and memory. Roberson found that reducing tau levels in tissues preserved the animals' ability to learn the maze, even though their beta-amyloid levels were high.

Another potential therapy is a peptide called NAP that has been shown to protect against beta-amyloid-induced neuron death.

In addition, Roberson found that tau reduction protected both transgenic and nontransgenic mice against something called excitotoxicity, which occurs when a type of amino acid in the brain becomes toxic to neurons. The study, published in *Science*, concluded that reducing tau can block both beta-amyloid and excitotoxic dysfunction in neurons.[6] Thus, tau reduction may represent an effective strategy for treating Alzheimer's disease and related conditions.

Another potential therapy is a peptide called NAP that has been shown to protect against beta-amyloid-induced neuron death. NAP appears to block the buildup of beta-amyloid into plaques and fibrils. It also binds to tubulin, thereby preventing the microtubule disruption associated with Alzheimer's.

Paul Aisen and his research team at Georgetown University studied transgenic mice that show both hallmarks of Alzheimer's: accumulation of beta-amyloid and the modified forms of tau associated with microtubule dysfunction. The team gave the mice daily doses of NAP for three months, beginning at age nine months—before disease symptoms appeared.

They reported in the *Journal of Molecular Neuroscience* that the treatment significantly lowered beta-amyloid levels in the animals' brains.[7] NAP also reduced levels of abnormal tau. The researchers conclude that NAP might offer promise as a treatment for Alzheimer's.

Meanwhile, researchers at the Massachusetts Institute of Technology studied mice in which they could control the loss of neurons in certain

places and for short periods. Some of the mice were placed in an "enriched environment"—their cages contained running wheels, toys, tunnels, and climbing devices. In this enriched environment, the mice regained their learning behavior and reestablished access to long-term memories, even after brain atrophy and neuronal loss had occurred.

The team studied the genetic material present in the brain tissue of the mice. The scientists were especially interested in the histone tails of chromatin, the complex of DNA and proteins that makes up chromosomes. Chromatin strands contain histones, a type of protein around which DNA coils. Histones are what primarily make up the tails, or ends, of chromatin strands.

The researchers found that chemical changes in these histone tails occurred when the environment was enriched. When those same changes were induced by a drug that inhibits the activity of a related enzyme called HDAC, dendrites sprouted, the number of synapses increased, and learning behavior and access to long-term memory improved. The researchers concluded in their May 10 *Nature* article that drugs that inhibit the enzyme might help in treatment of Alzheimer's and other forms of dementia.[8]

Other researchers are probing how HDAC enzyme inhibitors work. Do they alter the expression of many genes and affect memory processes in a general way? Or is their action targeted? One study found two specific effects. One relates to a protein called CREB, which is formed inside the neuron and is known to be important to memory formation. Inhibitors also affect the expression of several individual genes during memory consolidation.[9]

Predicting Alzheimer's

A team led by David Holtzman at Washington University in St. Louis reported in the *Archives of Neurology* in March 2007 that ratios of certain types of beta-amyloid and tau can help identify whether someone with normal cognition has amyloid deposits in the brain, increasing the chances that dementia will develop.

The researchers analyzed the cerebrospinal fluid and blood of 139 volunteers, ages 60 to 91, who had been diagnosed as cognitively normal or having very mild or mild dementia.[10] The team found that individuals with very mild or mild Alzheimer's have less of a certain type of beta-amyloid and more tau in their cerebrospinal fluid than healthy controls. Levels of this beta-amyloid type predicted

whether amyloid was present in the brains of people with and without dementia.

Remembering and Imagining

Also in 2007, a growing number of researchers explored the relationship between remembering the past and imagining the future. People who have suffered damage to the hippocampus have difficulty remembering past events and imagining future scenarios. People with schizophrenia also recall fewer specific past events and imagine fewer specific future events than do normal subjects, reported Arnaud D'Argembeau of the University of Liège in Belgium. The research is reported in the *Journal of Abnormal Psychology*.[11]

One result of the loss of episodic memory is that older adults sometimes have trouble integrating information and forming relations between items.

Similar findings emerged in a Harvard study reported in *Psychological Science*. A team of researchers studied episodic memory in healthy older adults and college students. Episodic memory is important because it allows the recall of personal incidents that uniquely define an individual's life. It lets people project themselves both backward and forward in subjective time.

When the team asked the volunteers to generate past and future events, the older adults came up with fewer episode-specific details relating to past events than younger adults did. The same effect occurred for future events: imagined happenings contained less episodic information.[12] One result of the loss of episodic memory is that older adults sometimes have trouble integrating information and forming relations between items.

Neuroimaging studies show evidence of shared brain regions for remembering the past and imagining the future. In one study, 21 volunteers raging in age from 18 to 32 underwent magnetic resonance imaging while remembering past events and imagining future events in response to event cues.[13] The scans revealed a striking overlap in the activity associated with past and future events: the processes of remembering the past and imagining the future are associated with a core brain system that includes the prefrontal and medial temporal

lobe regions, as well as posterior regions (including the precuneus and the retrosplenial cortex) that are consistently observed as components of the brain's memory retrieval network.

Findings such as these have led to the concept of the "prospective brain," the idea that the brain uses stored information to imagine, simulate, and predict possible future events. The concept offers a new way of thinking about and studying memory, according to Harvard psychologists Daniel Schacter, Donna Rose Addis, and Randy Buckner.[14] It suggests that both remembering and imagining use shared networks to retrieve stored information.

Imagining, however, requires the recombination of details in new ways, for which additional brain regions must be recruited. This overlap may explain why recall fails as a perfect recording of the past and functions instead as a constructive process. The ability to reorganize and reshape information stored in memory may be crucial to planning for the future, Schacter, Addis, and Buckner say.

NOTES

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THE DANA ALLIANCE FOR BRAIN INITIATIVES

Mission Statement, Goals, and Membership

Dana Alliance Vision Statement - 2001

Imagine a world…

- in which Alzheimer's, Parkinson's, Lou Gehrig's (ALS) diseases, and retinitis pigmentosa and other causes of blindness are commonly detected in their early stages, and are swiftly treated by medications that stop deterioration before significant damage occurs.
- in which spinal cord injury doesn't mean a lifetime of paralysis because the nervous system can be programmed to re-wire neural circuits and re-establish muscle movement.
- in which drug addiction and alcoholism no longer hold people's lives hostage because easily available treatments can interrupt the changes in neural pathways that cause withdrawal from, and drive the craving for, addictive substances.
- in which the genetic pathways and environmental triggers that predispose people to mental illness are understood so that accurate diagnostic tests and targeted therapies—including medications, counseling, and preventive interventions—are widely available and fully employed.
- in which new knowledge about brain development is used to enhance the benefits of the crucial early learning years and combat diseases associated with aging.
- in which people's daily lives are not compromised by attacks of depression or anxiety because better medications are being developed to treat these conditions.

Although such a vision may seem unrealistic and utopian, we are at an extraordinarily exciting time in the history of neuroscience. The advances in research during the past decade have taken us further than we had imagined. We have expanded our understanding of the basic mechanisms of how the brain works, and are at a point where we can harness the healing potential of that knowledge.

We have already begun to devise strategies, new technologies, and treatments to combat a range of neurological diseases and disorders. By setting therapeutic goals, and applying what we know, we will develop effective treatments—and, in some instances, cures.

For all that has been learned in neuroscience recently, we are learning how much we do not know. That creates the urgency to continue basic research that looks at the broader questions of how living things work. This will help to formulate the complex questions that lead to scientific discovery.

The coordinated work of thousands of basic and clinical scientists in multiple disciplines, ranging from molecular structure and drug design to genomics, brain imaging, cognitive science, and clinical investigation, has given us a pool of information that we can now use to build into therapeutic applications for all neurological diseases and disorders. As scientists, we will continue to move forward not just as individuals, exploring our particular areas of interest, but also in concert with colleagues in all areas of science, mining opportunities to collaborate across disciplines.

Public confidence in science is essential if we are to be successful in our mission. To this end we recognize that dialogue between researchers and the public will be essential in considering the ethical and social consequences of advances in brain research.

The Dana Alliance for Brain Initiatives and the European Dana Alliance for the Brain represent a community of neuroscientists willing to commit to ambitious goals, as seen in 1992 in Cold Spring Harbor, New York, where an American research agenda was set forth and again in 1997 when the newly formed European group followed suit with its own goals and objectives. Both groups now are moving to build upon gains made so far. We are setting new goals to guide what can be achieved in the near term, and project even further into the future. By allowing ourselves to imagine what benefit to humanity this new era in neuroscience is likely to bring, we can speed progress toward achieving our goals.

The Goals

Combat the devastating impact of Alzheimer's disease.

In Alzheimer's disease, a small piece of the protein amyloid accumulates and is toxic to nerve cells. The mechanism of this accumulation has been worked out biochemically and in genetic studies in animals. Using these animal models, new therapeutic drugs and a potentially powerful vaccine are being developed to prevent the accumulation of this toxic material or enhance its removal. These new therapies, which will be tried in humans in the near future, offer realistic hope that this disease process can be effectively treated.

Discover how best to treat Parkinson's disease.

Drugs that act on dopamine pathways in the brain have had significant success in treating the motor abnormalities of Parkinson's disease. Unfortunately, this therapeutic benefit wears off for many patients after 5–10 years. New drugs are being developed to prolong the action of dopamine-based treatments and to slow the selective loss of nerve cells that causes this disease. For those in whom drug therapies fail, surgical approaches, such as deep brain stimulation, are likely to be of benefit. Newer forms of brain imaging have made it possible to determine if these treatments are rescuing nerve cells and restoring their circuits back toward normal.

Decrease the incidence of stroke and improve post-stroke therapies.

Heart disease and stroke can be strikingly reduced when people stop smoking, keep their cholesterol levels low, maintain normal weight by diet and exercise, and when diabetes is detected and treated. For those with strokes, rapid evaluation and treatment can lead to dramatic improvement and less disability. New treatments will be developed to further reduce the acute impact of stroke on normal brain cells. New rehabilitation techniques, based on understanding how the brain adjusts itself following injury, will result in further improvement.

Develop more successful treatments for mood disorders, such as depression, schizophrenia, obsessive compulsive disorder, and bipolar disorder.

Although the genes for these diseases have eluded researchers over the past decade, the sequencing of the human genome will reveal several of the genes for these conditions. New imaging techniques, along with new knowledge about the actions of these genes in the brain, will make it possible to see how certain brain circuits go awry in these disorders of mood and thought. This will provide the basis for better diagnosis of patients, more effective use of today's medications, and the development of entirely new agents for treatment.

Uncover genetic and neurobiological causes of epilepsy and advance its treatment.

Understanding the genetic roots of epilepsy and the neural mechanisms that cause seizures will provide opportunities for preventive diagnosis and targeted therapies. Advances in electronic and surgical therapies promise to provide valuable treatment options.

Discover new and effective ways to prevent and treat multiple sclerosis.

For the first time, we have drugs that can modify the course of this disease. New drugs, aimed at altering the body's immune responses, will continue to decrease the number and severity of attacks of multiple sclerosis. New approaches will be taken to stop the longer-term progression caused by the breakdown of nerve fibers.

Develop better treatments for brain tumors.

Many types of brain tumors, especially those that are malignant or have spread from cancer outside the brain, are difficult to treat. Imaging techniques, focused-radiation treatments, different forms of delivery of drugs to the tumor, and the identification of genetic markers that will assist diagnosis, should provide the basis for development of innovative therapies.

Improve recovery from traumatic brain and spinal cord injuries.

Treatments are being evaluated that decrease the amount of injured tissue immediately after an injury. Other agents are aimed at promoting the rewiring of nerve fibers. Techniques that encourage cellular regeneration in the brain to replace dead and damaged neurons will advance from animal models to human clinical trials. Electronic prostheses are being developed that use microchip technology to control neural circuits and return movement to paralyzed limbs.

Create new approaches for pain management.

Pain, as a medical condition, need no longer be woefully undertreated. Research into the causation of pain and the neural mechanisms that drive it will give neuroscientists the tools they need to develop more effective and more highly targeted therapies for pain relief.

Treat addiction at its origins in the brain.

Researchers have identified the neural circuits involved in every known drug of abuse, and have cloned major receptors for these drugs. Advances in brain imaging, by identifying the neurobiological mechanisms that turn a normal brain into an addicted brain, will enable us to develop therapies that can either reverse or compensate for these changes.

Understand the brain mechanisms underlying the response to stress, anxiety, and depression.

Good mental health is a prerequisite for a good quality of life. Stress, anxiety, and depression not only damage peoples' lives; they can also have a devastating impact on society. As we come to understand the body's response to stress and the brain circuits implicated in anxiety and depression, we will be able to develop more effective ways to prevent them, and better treatments to lessen their impact.

The Strategy

Take advantage of the findings of genomic research.

The complete sequence of all the genes that comprise the human genome will soon be available. This means that we will be able, within the next 10 to 15 years, to determine which genes are active in each region of the brain under different functional states, and at every stage in life—from early embryonic life, through infancy, adolescence, and throughout adulthood. It will be possible to identify which genes are altered so that their protein products are either missing or functioning abnormally in a variety of neurological and psychiatric disorders. Already this approach has enabled scientists to establish the genetic basis of such disorders as Huntington's disease, the spinocerebellar ataxias, muscular dystrophy, and fragile-X mental retardation.

The whole process of gene discovery and its use in clinical diagnosis promises to transform neurology and psychiatry and represents one of the greatest challenges to neuroscience. Fortunately the availability of microarrays or "gene chips" should greatly accelerate this endeavor and provide a powerful new tool both for diagnosis and for the design of new therapies.

Apply what we know about how the brain develops.

The brain passes through specific stages of development from conception until death, and through different stages and areas of vulnerability and growth that can be either enhanced or impaired. To improve treatment for developmental disorders such as autism, attention deficit disorder, and learning disabilities, neuroscience will build a more detailed picture of brain development. Because the brain also has unique problems associated with other stages of development, such as adolescence and aging, understanding how the brain changes during these periods will enable us to develop innovative treatments.

Harness the immense potential of the plasticity of the brain.

By harnessing the power of neuroplasticity—the ability of the brain to remodel and adjust itself—neuroscientists will advance treatments for degenerative neurological diseases and offer ways to improve brain function in both healthy and disease states. In the next ten years, cell replacement therapies and the promotion of new brain cell formation will lead to new treatments for stroke, spinal cord injury, and Parkinson's disease.

Expand our understanding of what makes us uniquely human.

How does the brain work? Neuroscientists are at the point where they can ask—and begin to answer—the big questions. What are the mechanisms and underlying neural circuits that allow us to form memories, pay attention, feel and express our emotions, make decisions, use language, and foster creativity? Efforts to develop a "unified field theory" of the brain will offer great opportunities to maximize human potential.

The Tools

Cell replacement

Adult nerve cells cannot replicate themselves to replace cells lost due to disease or injury. Technologies that use the ability of neural stem cells (the progenitors of neurons) to differentiate into new neurons have the potential to revolutionize the treatment of neurological disorders. Transplants of neural stem cells, currently being done on animal models, will rapidly reach human clinical trial status. How to control the development of these cells, direct them to the right place, and cause them to make the appropriate connections are all active areas of research.

Neural repair mechanisms

By using the nervous system's own repair mechanisms—in some cases, regenerating new neurons and in others restoring the wiring—the brain has the potential to "fix" itself. The ability to enhance these processes provides hope for recovery after spinal cord injury or head injuries.

Technologies that may arrest or prevent neurodegeneration

Many conditions, such as Parkinson's disease, Alzheimer's disease, Huntington's disease, and ALS are the result of degeneration in specific populations of nerve cells in particular regions of the brain. Our present treatments, which modify the symptoms in a disease like Parkinson's disease, do not alter this progressive loss of nerve cells. Techniques that draw on our knowledge of the mechanisms of cell death are likely to offer methods to prevent neurodegeneration and, in this way, stop the progression of these diseases.

Technologies that modify genetic expression in the brain

It is possible to either enhance or block the action of specific genes in the brains of experimental animals. Mutated human genes that cause neurological diseases, such as Huntington's and ALS, are being used in animal models to assist in the development of new therapies to prevent neurodegeneration. Such techniques have also provided valuable information about normal processes, such as development of the brain, learning, and the formation of new memories. These technologies provide an approach to the study of normal and abnormal brain processes more powerful than there has ever been available before and, in time, may be used clinically in the treatment of many brain disorders.

Advanced imaging techniques

There have been remarkable advances in imaging both the structure and the function of the brain. By developing techniques that image brain functions as quickly and accurately as the brain does, we can achieve "real-time" imaging of brain functions. These technologies will allow neuroscientists to see exactly which parts of the brain are involved as we think, learn, and experience emotions.

Electronic aids to replace non-functional brain pathways

In time it may be possible to bypass injured pathways in the brain. Using multi-electrode array implants and micro-computer devices—which monitor activity in the brain and translate it into signals to the spinal cord, motor nerves, or directly to muscles—we expect to be able to offer the injured hope for functional recovery.

Novel methods of drug discovery

Advances in structural biology, genomics, and computational chemistry are enabling scientists to generate unprecedented numbers of new drugs, many of which promise to be of considerable value in clinical practice. The development of new, rapid screening procedures, using "gene chips" and other high throughput technologies, will reduce the time between the discovery of a new drug and its clinical evaluation, in some cases, from years to just a few months.

Our Commitment, Bench to Bedside

Today, neuroscience research benefits from an unprecedented breadth of opportunity. We have expanded our understanding of brain function, disease onset, and disease progression. A sophisticated arsenal of tools and techniques now enables us to apply our knowledge and accelerate progress in brain research.

As scientists, we are committed to continue making progress "at the bench." To attack major brain disorders, such as Alzheimer's, stroke, or Parkinson's, will require continued basic research from which clinicians can move toward development of new treatments and therapies. We have a responsibility to continue such research and to enlist its support by the public.

We also have the obligation to explain those areas of scientific research that soon may have direct application to human beings. To progress beyond laboratory research, we need to take the next clinical steps in partnership with the public—translating science into real and genuine benefits "at the bedside."

As our tools and techniques become more sophisticated, they may be considered threatening in their perceived potential for misuse. It is important to recognize the understandable fears that brain research may allow scientists to alter the most important aspects of our brains and behavior, changing the very things that make us uniquely human. Public confidence in the integrity of scientists, in the safety of clinical trials—the cornerstone of applied research—and in the assurance of patient confidentiality, must be continually maintained.

Putting research into a real-life context is always a challenge. People not only want to know how and why research is done, they also want to know why it matters to them. Allaying the public's concerns that the findings of brain science could be used in ways that might be harmful or ethically questionable is particularly important. Meeting both of these challenges is essential if those affected by neurological or psychiatric disorders are to reap fully the benefits of brain research.

Our mission as neuroscientists has to go beyond brain research. We accept our responsibility to explain in plain language where our science, and its new tools and techniques, are likely to take us. We, the members of the Dana Alliance and the European Dana Alliance willingly embrace this mission as we embark on a new decade of hope, hard work, and partnership with the public.

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