A NEUROSCIENTIST’S PERSPECTIVE ON THE ADVANCES IN THE GENETICS OF PSYCHIATRIC DISORDERS

Essay by Joseph T. Coyle, M.D.
THE DANA ALLIANCE’S 2010 PROGRESS REPORT ON BRAIN RESEARCH

Introduction by Steven E. Hyman, M.D.

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CONTENTS

1 Introduction
   by Steven E. Hyman, M.D.

8 A Neuroscientist’s Perspective on
the Advances in the Genetics of Psychiatric Disorders
   by Joseph T. Coyle, M.D.

PROGRESS IN BRAIN RESEARCH IN 2009

Chapter 1
17 Genetics: The Emerging Science of
Gene Expression and Mental Illness
   by Elizabeth Norton Lasley

Chapter 2
33 Deep Brain Stimulation: Beyond Movement Disorders
   by Brenda Patoine

Chapter 3
45 Parkinson’s Disease: A Paradigm Shift
   by Kayt Sukel

Chapter 4
59 Multiple Sclerosis: Genetic Studies
Begin to Unravel the Mystery
   by Tom Valeo

Chapter 5
71 Memory and Forgetting: Piecing Together
the Molecular Puzzle of Memory Storage
   by Sandra Swanson

Chapter 6
83 Neuroprotection: Guarding Against Injury and Degeneration
   by Scott Edwards

Chapter 7
93 Roundup: Other Important Findings in 2009
   by Maria Turner

101 Notes

113 Index
INTRODUCTION

Steven E. Hyman, M.D.

Since its formation in 1992, the Dana Alliance for Brain Initiatives has sought to keep the public informed about cutting-edge research in neuroscience. Given the large and growing number of people afflicted with brain disorders, public understanding of the research becomes more crucial each year.

Among the important findings of the past year presented in this, the sixteenth in the Alliance’s annual progress reports on brain research, I want to highlight promising outcomes in the genetics of neuropsychiatric disorders. I do this not only because of the significance of the results, but also because they arrive after years of frustration.

Neuroscientists face daunting challenges in attempting to understand the processes that go awry in the brain to cause autism, schizophrenia, bipolar disorder, obsessive-compulsive disorder, depression and other neuropsychiatric disorders. The difficulty derives in part from the fact that these disorders affect the high-level integrated functioning of the human brain, impairing complex domains such as social cognition, control of behavior and mood regulation. Consequently, it has been very difficult to model these disorders convincingly in animals. In addition, rather than exhibiting readily identifiable pathology such as cell death, the symptoms of neuropsychiatric disorders often reflect abnormal activity in brain circuits. In psychiatry, for example, the science has matured to the point that depression is no longer seen in excessively simplistic terms as the deficiency of one or two neurotransmitters; rather, it is viewed as the result of regulatory mechanisms in the brain gone awry.

Non-invasive neuroimaging provides some assistance, by enabling researchers to observe the brain at work while performing tasks that might help distinguish between health and disorder or probe specific impairments in conditions such as autism or schizophrenia. With imaging, it has been possible to study, for example, how people with autism process social information and to study how the impairment of
“working memory,” which is the ability to hold information “online” to guide thought and behavior, affects people with schizophrenia. A more recent development, deep brain stimulation (DBS), described in this report, promises to give us new information on the workings and possible infirmities of brain circuits that regulate mood and aspects of cognition. By delivering electrical current through fine electrodes implanted deep in the brain, DBS can activate or inhibit specific brain circuits and thus regulate mood or diminish unwanted, intrusive thoughts (obsessions). The combination of results from neuroimaging and DBS has given us exciting new hypotheses about the circuits that regulate mood in the brain and those that might malfunction, for example, to cause depression or obsessive-compulsive disorders. Nonetheless, these are only pieces in an extraordinarily complex puzzle.

Scientists have long hoped that the identification of the precise genetic variations that contribute to neuropsychiatric disorders would provide tools that neurobiologists could use to decipher the disease processes. Though finding such genes has proved difficult (for reasons that I will describe below), nevertheless, after years of frustration, results reported during the last year have begun to identify genes involved in autism and, with a bit less certainty, in schizophrenia and bipolar disorder.

An important distinction is also relevant to this research: the distinction between genetics and epigenetics, both of which produced significant new findings in psychiatric research in 2009. Briefly, epigenetics is the study of how the action of genes may change once an organism’s underlying DNA blueprint is laid down. Here’s what that means: DNA, the genetic material, is bound inside the nucleus of the cell by a large diversity of proteins. If uncoiled, DNA molecules would stretch far beyond the boundaries of individual cells, but they do not, because they are held in coiled and folded conformations by histones and other proteins. As a kind of spool for the DNA, histones are the most important in holding its structure. If a gene is to be expressed—that is, to be read out to produce either an RNA or a protein product—it must be accessible to the transcriptional machinery that does the reading, and histones help make that possible, too. We have long known that both DNA and histones undergo chemical modification (e.g., by adding or removing methyl groups or other chemical groups) and that these modifications make it more or less likely that a nearby gene will be expressed. The modification of DNA and histones is what is meant by epigenetic regulation of the genome.
Most of the attention paid to epigenetics was focused on early development. Every cell in our bodies begins with the same genome, but some become liver cells; others become one of many thousands of different types of neurons; and still others take on the humble but necessary task of making fingernails. The stable patterns of gene expression that give rise to the myriad cell types of the body are in great part the result of epigenetic modifications within cells. A surprise that crystallized in the recent past is that epigenetic regulation can be induced by stress, other types of life experience and both therapeutic and abused drugs. The implications of these discoveries are now a matter of very exciting research, and one possibility is that epigenetic mechanisms may provide new avenues for designing treatments.

Genetics provides tools for biological investigation in many ways. At the simplest level, a version of a gene that predisposes to a disease, such as autism, can be compared with a different version of the same gene that does not. If that particular genetic variant strongly influences the symptoms of autism (i.e., the variant’s degree of “penetrance”), researchers might insert it into a mouse genome to observe its effect on brain development, brain function and behavior in the engineered mice.

Despite the substantial influence of genes, attempts to identify the variants that confer risk of neuropsychiatric illness have proved frustrating for the last two decades. This is largely because the concept of heritability that we investigate is an aggregate measure—it lumps together the totality of the effects of genetic influence. If we “look under the hood,” we find that a very large number of different genes affecting brain function can contribute to specific disorders, and that, in different families, an individual might have symptoms of schizophrenia as a result of different combinations of genes. This scientifically messy situation, which is described as “genetic complexity,” is typical of most common human illnesses. Harmful mutations that act alone to cause a serious illness tend to decrease reproductive fitness, and thus they often get weeded out of the gene pool. As a result, disorders caused by a single harmful high-penetrance mutation tend to be rare. If, instead, illness is caused by the interaction of a large number of gene variants that are not harmful, except in unlucky combinations, the risk-conferring gene variants will remain in the population. This is described as the “common disease, common variant” hypothesis. Alternatively, disorders that appear genetically complex can
result from diverse high-penetrance mutations, each individually rare, acting in different extended families. Thus, for example, a disorder causing vision loss, retinitis pigmentosa, is a single-gene disorder in each extended family, but there are a very large number of individual mutations that lead to retinal degeneration, ultimately by converging molecular mechanisms.

Modern genomic technologies have begun to solve the genetics of diseases resulting from both types of complexity, but the common neuropsychiatric disorders exhibit one further level of difficulty to geneticists. Unlike most other complex diseases, such as type 2 diabetes mellitus or inflammatory bowel disease, no objective medical tests exist to narrow the study populations of neuropsychiatric disorders. Geneticists—indeed, all scientists studying these disorders—must therefore rely on clinical observation, with all its inherent imprecision, to make diagnoses.

After years of taking one step forward and one step back, research efforts in 2009 yielded notable progress in the search for genetic variants that contribute to autism and promising results for those involved in schizophrenia and bipolar disorder. I readily confess that this work is far from complete and, in most cases, still some distance from providing the tools that neurobiologists need to interrogate the brain. However, the sense of progress and promise is palpable and exciting.

The Human Genome Project and other large-scale efforts in genomics have provided new information and technologies relevant to understanding disease risk. Although I am not a human geneticist, I have long been concerned with the question of how to exploit the high heritability of neuropsychiatric disorders to provide tools for neurobiology. A decade ago, when I was director of the National Institute of Mental Health (NIMH), the reality of genetic complexity and the challenges it posed were coming squarely into view. Traditional linkage studies, based on markers taken from low-resolution maps of the genome, were not yielding reproducible results. The question was how to spend federal resources in a way that would maximize the possibility of long-term success. I began programs to collect and store DNA samples and extensive phenotype information from large numbers of individuals and families affected by schizophrenia, bipolar disorder, early onset depression and later, in collaboration with family groups, autism. I also instituted a “sharing policy” so that these resources could be available broadly
to researchers as the technologies improved. The sharing policy was not initially popular with the entire community of investigators, but it is now widely accepted. As the psychiatric research community matured, it was widely recognized that pooling of samples would be necessary to generate studies large enough to yield reproducible results. Not surprisingly, many of the recent successes have come from large international collaborations.

It has taken far longer than I could have imagined to get to where we are now, and the NIMH DNA resources have proven important but far too small on their own. As I have described, it is clear that multiple pathways lead to illnesses such as autism and schizophrenia; some individuals are at risk because of an unlucky combination of a very large number of common genetic variants, and others may have rare harmful mutations. Perhaps not surprisingly, the discovery of common variants has led to a new controversy: since each variant has such a small individual influence, one can reasonably ask whether the results of whole-genome association studies can really inform biology. I believe that there will be a large biological payoff, but that it will require very clever scientists, including computer scientists, to show us how all this information comes together.

If the genetic clues converge on a limited number of pathways that can illuminate the biology of the illness, clues to treatment developments will follow. Unfortunately, there are no guarantees that this will happen. The discovery of rare high-penetrance mutations may initially be more useful to neurobiologists, because such mutations are more likely to produce substantial biological effects. Already researchers have produced genetic mouse models with human mutations that cause autism or disorders that include symptoms of autism, such as Rett syndrome. I do not want to over-promise on the rate of progress, but I think that, after decades of effort, we will have a new and important window into the biology of neuropsychiatric disorders. This will be complemented by new understandings of the role of epigenetics and by new avenues of research on the brain.

One such avenue described in this report brought good news to scientists pursuing treatments for disorders that do not respond to pharmacological therapies: encouraging results from deep brain stimulation (DBS) studies. DBS involves neurosurgery to implant thin electrodes deep in the brain, attaching them to a device implanted under the collarbone that delivers a steady electrical current to the neurons the electrodes are touching. Developed in the late 1980s
and 1990s, DBS is now widely used to treat symptoms of treatment-resistant Parkinson’s disease and is approved by the FDA on a limited basis for obsessive-compulsive disorder, as well as some movement disorders. New studies are showing that some patients with depression who had not responded to medication, psychotherapy and electroconvulsive therapy (shock treatment) have experienced long-lasting improvements with this therapy.

Beyond the value of genetics for psychiatric research, genetic advances in 2009 continued to improve the outlook for new therapies for diseases, such as multiple sclerosis, in which multiple genes are implicated. Certain populations, especially those of Northern European stock, are more susceptible to MS, but environmental pressures such as a virus may be needed as a catalyst. Once scientists are able to determine which genes are interacting with which environmental factors, new treatments will become possible. In 2009, scientists using a genome database identified several specific genes, all genes in the immune system, that contribute to susceptibility to MS.

Equally noteworthy in 2009 were findings about molecular processes providing insight into normal brain function. Among these, scientists studying the molecules involved in memory succeeded in selectively removing fearful memories in rats by using a protein, CREB, to identify the specific neurons carrying the memory, and then destroy those neurons. Other research explored enhancing memories by increasing the expression of an enzyme, PKM zeta, which helps turn short-term memories into long-term memories.

Against the backdrop of debilitating disorders and those that threaten people’s very identity, it is easy to forget that, for most people, the risk is that harm to the brain will come in the form of disabling brain or nervous system injury, by stroke, accidents such as car crashes and chronic disease. In the search for effective therapies and treatments for injury and disease, scientists have begun delving into the mystery of neuroprotection—the methods by which neurons protect themselves against injury. In 2009 scientists added several chemicals to the small list of known neuroprotectors. Sex hormones, especially estrogen, figure heavily in the reduction of neuron loss with aging, while vitamin D helps to minimize cognitive decline.

But it was genetics that took center stage in the advancement of neuroscience in 2009. Genes dictate how our brains develop, what diseases we may be susceptible to and even how well our neurons will survive into old age. Mutations and variants, which scientists are
now able to identify through the use of the Humane Genome Project, hold clues to treating psychiatric illnesses, such as Parkinson’s, and to unlocking cures for diseases such as multiple sclerosis. In combination with the discoveries of the molecules that govern brain function, genetics promises to propel neuroscientists to greater understanding about how the brain works, and how we can both heal it and improve its function.
As a neuroscientist, I would have thought that the rules of genetics were “settled law” and that dissecting the genetics of psychiatric disorders was simply a matter of investing the time and effort. To the contrary, this year has provided a metaphorical splash of cold water in my face, reminding me that science is never as simple as it seems. Specific noteworthy advances include the findings that methods used successfully to identify genes responsible for many heritable disorders were shown not to be applicable for identifying genes responsible for psychiatric disorders, that new mutations may be a frequent cause of psychiatric disorders and that early life experiences can alter gene function throughout life in ways that have substantial behavioral consequences.

Genetics and Brain Disorders

Many rare brain disorders exhibit “Mendelian” inheritance, so named after the monk Gregor Mendel, who first described dominant and recessive patterns of inheritance in the colors of pea flowers. For example, Tay-Sachs disease is inherited via an autosomal recessive gene, meaning that a sibling has a 25 percent risk of also having the disease. Familial amyotrophic lateral sclerosis (ALS) is inherited via an autosomal dominant gene, meaning that a sibling or offspring has a 50 percent risk. In contrast, the heritability of psychiatric disorders is much less clear-cut.

Although by the late nineteenth century, psychiatrists were aware that psychotic disorders appeared to occur more frequently in families where a relative was affected, the study of the genetics
of psychiatric disorders was neglected for nearly a century. This situation developed because the concept of heritability of psychiatric disorders fell out of favor as the popularity of psychoanalytic theory rose in American and then European psychiatry. The fact that serious mental illness seemed to be concentrated in certain families was entirely consistent with psychoanalytic theory, in which the origin of mental illness was thought to be based on adverse early (parenting) life experiences.

Then, fifty years ago, researchers rigorously examined the heritability of schizophrenia by exploiting the fact that identical twins have essentially the same genomes, whereas fraternal twins do not. The relative contribution of environment versus genetics can be inferred from how far the rate of concordance—that is, the presence of the same trait or disorder in twin siblings—deviates from that predicted if the disorder were completely based on genetics (i.e., 100 percent concordance for identical twins if one is affected). The evidence showed a concordance rate of approximately 50 percent in identical twins when one was affected with schizophrenia. The concordance rate was about 10 percent in fraternal twins, who share half their genes. Still, psychiatry resisted the obvious inference of the heritability of schizophrenia because the finding could be explained by the assumption that identical twins would be treated much more alike by their mother than fraternal twins, thereby increasing “concordance.”

To address these reservations, Seymour Kety and his colleagues carried out a heroic study nearly forty years ago assessing the risk for schizophrenia in Scandinavian adopted offspring: the adult psychiatric status of children who had one parent suffering from schizophrenia was compared with the risk for adopted children whose biological parents were free of mental illness but whose adoptive family had one parent who had been diagnosed with schizophrenia. This human “cross-fostering” experiment, possible only because of the detailed and lengthy records maintained by the Swedish Health Ministry, demonstrated that the risk for schizophrenia was significantly higher in the offspring with a schizophrenic biological parent. Children adopted into families with a schizophrenic adoptive parent showed no greater incidence of schizophrenia than the general population. This study did much to undermine the belief that schizophrenia was merely a psychologic maladaptation. Rather, it supported the notion that the disorder involved substantial genetic, i.e., inheritable, risk factors.
As the twin paradigm became more accepted, it was quite helpful in clarifying the role of genes in the risk for autism. Leo Kanner first described autism in 1943, when he also noted that the parents of some afflicted children appeared to be aloof and rigid. Psychoanalytic theorists identified the “refrigerator mother” as the cause of autism in the children. However, twin studies demonstrated a remarkably high heritability, with 90 percent concordance of autism in identical twins when one was affected, but only 4 percent concordance in fraternal twins. Here, too, the results of twin studies eliminated maternal-infant interactions as responsible for a severe psychiatric disorder.

Components of the autistic phenotype (observable characteristics) can be seen more frequently in the parents and sibs (first-degree relatives) of individuals with autism than in the general population. These component symptoms, called endophenotypes, are thought to reflect the impact of shared risk genes. For example, deficits in social language similar to those occurring in autism—although much less severe—are found more frequently in parents with an autistic child than in parents of children without autism.

The high concordance rate in identical twins coupled with the rapid falloff in risk for first-degree relatives in autism (4 percent) and schizophrenia (10 percent) reveal a non-Mendelian pattern of genetic transmission (i.e., inconsistent with autosomal dominant, recessive or sex-linked genes). Thus, by the turn of this century, the genetics of psychiatric disorders began to look more like those of other common medical disorders, such as hypertension and diabetes mellitus, than like rare neurologic disorders. These common medical disorders involve complex genetics in which multiple risk genes of moderate effect interact with the environment to cause the disorder. Risk genes increase the likelihood of developing the disorder but do not cause it in the absence of other risk factors.

Candidate Genes Versus Whole Genome-wide Association Studies

The search for genes that cause psychiatric disorders began in earnest more than a decade ago. Researchers took advantage of their knowledge of the biochemical and cellular abnormalities that had been identified in the postmortem studies of the brains of individuals who died with specific psychiatric disorders. Plausible pathways of
pathology in schizophrenia, for example, include abnormal neural development and aberrant neurotransmission involving dopamine, GABA and glutamate. Genes encoding proteins involved in these pathologic processes were considered “candidate genes,” which is to say, genes likely to be mutant in the disorder. As precedent, the candidate gene strategy was the basis for the successful identification of risk genes for Alzheimer’s disease because of their role in the disposition of the pathogenic peptide, beta-amyloid.

Scientists identified single-nucleotide polymorphisms (SNPs)—places in the DNA where individuals differ with regard to a given nucleic acid—in potential candidate genes and looked for preferential transmission of those SNPs within families that had members affected by the disorder. These studies were conducted with dozens, then hundreds of participants. Well over twenty candidate genes were implicated by this strategy. However, a disconcerting lack of reproducibility among studies became apparent.

Given the estimates of the attributable genetic risk suggested by these positive results (much less than 25 percent), geneticists argued that the studies were statistically underpowered (i.e., had an insufficient number of subjects) to make legitimate comparisons and would therefore predictably yield false positive and false negative results. On the basis of studies of diabetes, another disorder of complex genetics, it was estimated that the number of affected subjects and controls by necessity would be in the range of several thousands to generate statistically meaningful results.

To counter the biases inherent in candidate gene studies, scientists proposed the genome-wide association study (GWAS), a method that scans the entire genome in an unbiased manner to identify any SNPs associated with the disorder—not just those located in potential candidate genes. Recently, GWAS studies have been published on schizophrenia and on autism that have used thousands of subjects. Results of the GWAS studies on schizophrenia were mixed. Despite the large number of subjects, researchers could confirm only a few of the putative risk genes identified during the last decade. However, the GWAS studies did identify new risk genes, and some of these seemed consistent with current hypotheses about the pathophysiology of schizophrenia. Two genes could affect brain development, and two other genes could affect the function of the neurotransmitter glutamate.

The limited success of these endeavors has convinced scientists that substantive advances in the genetics of psychiatric disorders will
require considerable cooperation among investigators to assemble the large number of genotyped subjects required. To that end, disease-specific data repositories have been developed with a compilation of genetic findings, such as that provided by www.szgene.org. In this way, it will be possible to accumulate genotypes on tens of thousands of subjects to achieve the requisite statistical rigor. Perhaps as the number of subjects increases, previously identified candidate genes will be confirmed with expanded GWAS.

Another source of concern about the candidate gene approach for psychiatric disorders comes from the recent discovery of a high concentration of copy number variations (CNVs) in the genomes of patients with psychiatric disorders. A CNV results from either deletions or duplications of stretches of DNA, which involve several genes. It has long been known that a rare, small deletion on chromosome 22q11, which causes velocardiofacial syndrome—a condition resulting in abnormal development of the parathyroid gland, thymus and heart—is associated with an increased risk for psychosis. Chromosome 15q11-13 deletions are associated with the developmental disorder Prader-Willi Syndrome; and genes such as neurexin 1, which are located within this deleted region, have been associated with risk for autism spectrum disorders (ASD). Given these findings, Jonathan Sebat and colleagues at the Cold Spring Harbor Laboratory wondered whether spontaneous CNVs in the genome might account for “sporadic” autism, a form in which no other family members are affected and thus one that is less likely to have a genetic basis. The researchers found that CNVs occurred in 10 percent of the sporadic autistic subjects, 3 percent of autistic subjects with an affected first-degree relative and only 1 percent of controls. A recent study involving nearly 2,500 autistic patients and controls supported these findings. Studies in individuals with schizophrenia have demonstrated that CNVs are three times more likely in those with the typical onset in their late teens or twenties than in people who do not have the disorder, but four times more likely in patients who have early-onset schizophrenia, which develops in young adolescence and sometimes sooner. These results suggest that new mutations are a much more significant factor in the causes of schizophrenia and autism than previously thought.
Epigenetics

The French naturalist Lamarck proposed that acquired traits such as the long neck that a giraffe develops from stretching for leaves in tall trees could be transferred to its offspring. This theory was discarded with the ascendance of Darwin’s theory of natural selection. However, recent research is showing that the genome can be modified by environmental events, thereby altering gene expression. This process, known as epigenesis, refers to alterations in gene function caused by mechanisms other than changes in the gene’s DNA sequence. Epigenetic changes of a gene can result in persistent alterations in its expression and thereby the physical traits, or phenotype, associated with that gene. These epigenetic changes in the gene can even be inherited by future generations. Recent advances suggest that epigenetic mechanisms may have robust effects on the manifestation of psychiatric disorders.

An intriguing and compelling story has emerged on how epigenetics may mediate the persistent effects of adverse experiences early in life. From biblical times through the elaboration of psychoanalytical theory by Sigmund Freud, it has been recognized that abuse and neglect in early childhood are associated with an increased risk of anxiety disorders, depression and even suicide in adulthood. This vulnerability has been linked to a dysregulation of the hypothalamic-pituitary-adrenal axis (HPA), which mediates the body’s stress response. The hypothalamus, pituitary and adrenal glands orchestrate the “fight or flight” response to acute stress. In normal individuals, they release the stress hormones the body needs to face or flee the threat and then abate the response when the danger is past. Key to this process are glucocorticoid receptors in the brain. These monitor levels of the stress hormone corticosterone and enable the signals that turn the stress response up or down. Persistently high levels of stress, particularly during infancy and childhood, disrupt this homeostatic feedback loop such that the individual becomes hyper-responsive to a given level of stress, with excessive corticosterone secretion. In fact, this dysregulation appears to be a major contributing factor to the high risk for depression in adults who experienced abuse and neglect in childhood.

Michael Meaney and his colleagues at McGill University have been exploring the molecular mechanisms that underpin persistent dysregulation of the HPA axis due to stress early in development. Mother
rats frequently groom and lick their pups during the first week after birth. Pups of mothers who engage in these behaviors rarely grow up to be hyper-responsive to stress. Meaney and his colleagues showed that the licking and grooming stimuli increased serotonin release in the hippocampus of the pups. Serotonin stimulates the expression of a transcription factor known as NGFI-A that binds to the promoter region of the gene for the glucocorticoid receptor (Nr3c1), thereby causing more receptors to be made. They found that the promoter region of the glucocorticoid receptor gene of adult rats that had been infrequently groomed and licked as pups was blocked by methylation, a chemical change of the nucleic acid cytosine. The blocked promoter was no longer responsive to NGFI-A, so fewer glucocorticoid receptors were made, causing persistent hyper-responsiveness to stress.

Meaney and his colleagues wondered whether similar results of early-life neglect played out in the human brain. To this end, they studied the status of the glucocorticoid receptor gene in the hippocampus of twelve individuals who committed suicide as adults and who had a history of serious child abuse, twelve who committed suicide without evidence of child abuse and twelve non-psychiatric controls who died suddenly. The expression of the glucocorticoid receptor was significantly reduced in suicides with the history of child abuse as compared with the two types of controls. They examined the glucocorticoid gene (Nr3c1) in the human homolog of the promoter region implicated in the rats and found that in the suicides with a history of child abuse there was significantly greater methylation and reduced expression of the glucocorticoid receptor, as compared to the two types of controls. Thus, the findings from a rodent model were successfully extended to humans. How the chemical changes of that particular brain region might lead to suicide, however, remains a subject of further study.

MicroRNAs

Recent research has identified another novel mechanism whereby small RNAs known as microRNAs (or miRNAs) regulate the synthesis of proteins by affecting mRNAs, which carry the blueprint from the DNA to the protein building site. miRNAs were first discovered fifteen years ago in the nematode *c. elegans*. The DNA sequences encoding these miRNAs are located in regions of the genome that do
not contain genes and were therefore thought to serve no function. Their role in mammalian gene expression is just now emerging, with more than half the scientific reports on the subject appearing within the last eighteen months. The miRNA binds to a complementary site on a targeted mRNA, thereby blocking the mRNA's ability to make protein or accelerating its degradation. In this way, the miRNA regulates the expression of the gene's protein product. More than one thousand distinct miRNAs have been identified, half of which are expressed primarily or exclusively in the brain.

Because individual miRNAs may have hundreds of potential mRNA targets, it is hypothesized that a specific miRNA might be involved in coordinated regulation of protein expression in functional networks such as those regulating brain development or synaptic plasticity. Because of the abundance of miRNA genes, it is now appreciated that genetic “hot spots” such as 22q11 for schizophrenia might be linked to miRNA genes and not just protein-coding genes. John Rubenstein, a child psychiatrist at the University of California, San Francisco, has noted that the chromosomal 8p region, which contains a number of genes associated with risk for psychiatric disorders, also encodes at least 8 miRNAs. Thus, non-coding regions of the genome, until recently thought to be functionally unimportant, actually harbor miRNA genes that can have substantial impact on brain function and disease processes.

**Conclusion**

What can we take away from these remarkable advances in our understanding of the molecular genetics of psychiatric disorders? First, it is apparent that the established research strategies for studying Mendelian disorders are simply inadequate for the complex genetics of psychiatric disorders such as schizophrenia, autism and depression. Individual laboratories working with a few hundred subjects are unlikely to succeed in identifying risk genes for these illnesses. Rather, we need large consortia that are able to collect thousands of subjects and study their genetics. Open databases must serve as repositories for the genotypes for specific disorders and should provide the most current summary of risk genes and CNVs.

Second, researchers must pay greater attention to the influence of epigenetics on behavior. Meaney’s corpus of research on
the glucocorticoid receptor and anxiety is a wonderful example of how focusing on a particular behavioral phenotype can ultimately be highly informative. Nevertheless, his research addresses only one region of a single gene. The possibilities of environmental-gene interactions combined with gene-gene interactions that impact behavior seem immense.

Given these genetic advances, we have much to look forward to in the coming years. But no one knows what additional surprises lurk in the human genome, like the recently described CNVs and miRNAs, that will further disabuse us about simplistic hypotheses as to the causes of psychiatric disorders.
Nuala Sykes analyzes DNA sequence electropherograms in the Wellcome Trust Centre for Human Genetics.  
(Courtesy of Anthony Monaco / Wellcome Trust Centre for Human Genetics)
Advances in 2009 cast light on the mystery that enshrouds the genetics of mental illness. A convergence of scientific insight and increasingly sophisticated technology is allowing scientists to peer deeper into DNA, finding mutations that may help uncover the underpinnings of brain dysfunction in psychiatric disorders.

Several studies during the year revealed genetic mutations that may lead to new ways to approach schizophrenia. Others may help explain why autism is a central feature of many syndromes that in other respects differ greatly. Yet another study showed that adverse experiences in childhood can lead to “epigenetic” changes—actual changes to one’s genetic makeup that creep in during the process of converting DNA code into a functional protein—resulting in the seeming paradox of an environmentally induced genetic condition.

“The power of genetics is now so advanced that we can check many pieces of the genome to find rare mutations and variants that, together, may lead to new understanding,” said Scharahm Akbarian of the University of Massachusetts.

Akbarian compared the advances in recent years to the evolution of Google Earth, which began as a series of satellite images of the planet. “Now you can use Google Earth to find an intersection in a town. In the same way, we can scan larger pieces of DNA faster than ever, finding lots of candidate regions involved in brain disorders. And a very encouraging development is that some of these regions are being replicated in different groups of subjects.”

Setting the Stage for Genetic Breakthrough

New understanding is sorely needed in a field where no new therapies have emerged for several decades. The medications used to treat psychiatric illness still attempt to adjust the balance of brain chemicals such as dopamine and serotonin. But most take weeks to have an effect and come with severe side effects, not to mention that, always, a significant number of patients fail to find any benefit.

The 1990s saw an intensified search for “culprit genes” involved in brain disorders and many other illnesses. The approach was to identify susceptibility genes among patients with a particular disease, use the genes to develop animal models and identify the molecular pathways involved, thus leading to possible therapies such as developing a custom-designed or “monoclonal” antibody or other therapeutic
compound to block the effects of the malfunctioning gene’s protein product. In Alzheimer’s disease, for example, the discovery of the amyloid precursor and presenilin genes have pointed to molecular pathways involved in the disease, as well as to several potential drug targets.

In general, though, the paradigm has not held up for neuropsychiatric disorders, due to what Harvard University’s Steven Hyman calls the “fiendish complexity” of the underlying genetics. Similar symptoms can result from different genetic risk factors; or, conversely, individuals with the same genetic variant can have different DSM-IV diagnoses or show no symptoms at all. In one large family, for example, a disrupted gene on chromosome 1 can lead to schizophrenia, the comparatively milder form known as schizoaffective disorder, bipolar disorder or major depression.

According to Douglas Levinson of Stanford University, some of the first hunts for “culprit genes” in mental illness looked for genes involved with the chemical messengers that were targeted by the available drugs—schizophrenia, for example, is still treated with dopamine blockers—yet none of these genetic dragnets yielded candidate genes of any statistical significance. Now, however, new insights are appearing at levels of precision that would not have been possible without the convergence of knowledge, procedures and technology that enabled researchers to find needles in the haystack of the genome.

In 2001, the entire human genome (the complete sequence of human DNA) was published in a worldwide effort appropriately named the Human Genome Project.

“The Human Genome Project sparked an intense wave of competition among biotechnology companies to develop ‘microarrays’ on each colored spot on a microarray is associated with a different gene. The different colors represent either healthy (control) or diseased (sample) tissue. The location and intensity of a color shows whether the gene, or mutation, is present in either the control and/or sample DNA, and its level of expression. (National Medical Library)
which a million or more genetic variants could be tested or assayed,” said Levinson. “Meanwhile, clinicians had to find ways to recruit not just hundreds but thousands of people with schizophrenia. Finally, computers had to be sophisticated enough to handle the data. When the first search for schizophrenia genes began, back in the 1990s, the average hard drive was 32 megabytes. Today one of our files wouldn’t even fit on a hard drive that size, never mind the software needed to analyze all the data.”

**Misspellings in the Code**

Some of the first clues to result from the Human Genome Project were minute changes called single-nucleotide polymorphisms, abbreviated as SNPs and pronounced “snips.” A further research push, the International HapMap Project, cataloged about three million SNPs between 2005 and 2007.

SNPs are genetic differences between individuals at the level of one “letter” in the genetic code. This code consists of long chains of four “bases,” or building blocks, called nucleotides—adenine, guanine, cytosine and thymine, each abbreviated by its first letter—held together in pairs by chemical bonds that twist the chain of DNA into its famous double-helix shape. A SNP is a substitution of one of these four letters with another. These differences are thought to account for genetic diversity as well as susceptibility to disease. Though other discoveries in recent years show that SNPs are not the whole story, they remain a promising line of research for understanding how a disease works.

Three papers published in the July 1, 2009, issue of *Nature* uncovered a trove of SNPs that may help explain the development of schizophrenia.

Each study was a genome-wide association scan—a systematic search for common SNPs that influence a disease or trait—led by an international consortium of scientists. Because the three groups shared their results, cross-checking their findings with the other groups’ patient samples to make each study a large “meta-analysis,” the number of subjects ultimately totaled more than 8,000 patients with schizophrenia and 19,000 controls (individuals without the disease).

The pooled results of the three studies turned up seven SNPs in an area on chromosome 6 that contains many genes involved in
Infection and immunity. Chromosome 6 hosts genes involved in the major histocompatibility complex (MHC), a set of proteins found on all cells, which signal to the immune system whether the cell is “self” or “non-self.” If the MHC binds to a non-self entity, such as a virus, the immune system launches its attack.

All three studies, individually and collectively, implicated the MHC—an intriguing finding since infection during pregnancy has long been suspected as one aspect of the prenatal environment that can increase risk for schizophrenia.

In a study by the Molecular Genetics of Schizophrenia (MGS) consortium, the SNPs identified were near a cluster of histone protein

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Single-nucleotide polymorphisms (SNPs) are genetic differences between individuals at the level of one “letter” in the genetic code. Because of base pairing, both nucleotides must change. In frame 2, the original “CTA” (frame 1) becomes “TTA” and “GAT” becomes “AAT.”

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genes, which form a structure for DNA molecules and can be chemically modified to alter the expression of other genes.\(^2\) (Histones have another, lesser-known role in antibacterial defense.)

The MHC was implicated in another study, published by the Sgene Consortium with Kari Stefansson of deCODE genetics, a Reykjavík, Iceland–based pharmaceutical company, as lead author. A genome-wide scan of their own 13,000 patients and more than 2,500 controls, plus meta-analysis of patients from all three studies, detected an even stronger “signal” closest to a specific gene, called PRSS16, which is located in a cluster of histone genes and is involved in immunity. The Sgene study also identified sites on chromosomes 11 and 18 that are involved with brain development and memory.\(^3\)

“We have to keep an open mind in schizophrenia research,” Levinson, a member of the MGS and study coauthor, said. “What if we eventually find that an abnormal response to an infection increases one’s risk of schizophrenia, as some researchers have suggested? Maybe that will lead to strategies for preventing schizophrenia in some people by preventing certain infections. But other findings suggested abnormalities in the development of brain cells. We still have a lot to learn.”

The third study, presented by the International Schizophrenia Consortium, also pointed to the MHC, finding significant overlap in gene variants that increase the risk for schizophrenia and bipolar disorder, but it found no overlaps with a host of non-psychiatric disorders, including hypertension and type 2 diabetes—indicating that these SNPs were specific signals for vulnerability to mental illness. This study also described a statistical model for deducing, on the basis of SNPs already identified, that a large set of common SNPs—most of them unknown at present—could account for at least 33 percent of risk.

The authors wrote that their model “suggests that genetically influenced individual differences across domains of brain development and function may form a [predisposition] for major psychiatric illness, perhaps as multiple growth and metabolic pathways influence human height.”\(^4\)

SNPs are providing other clues as well. In the August *Molecular Psychiatry*, other teams led by Levinson published a genome-wide linkage scan, plus a meta-analysis of a larger population, pointing to several chromosomal regions that might contain genes that play a role in schizophrenia.\(^5,6\) Unlike a genome-wide association scan,
which compares the genomes of individuals with and without a given disorder, a linkage scan concentrates on families in which two or more people have the disease, looking for “marker” locations that are near disease-causing variants. When a marker is found near another variant in many families affected by a disease, more often than might be expected by chance, this “linkage” is thought to signal a nearby disease-related gene.

Levinson explained that while association studies cast a wider net in terms of finding more of the “common” SNPs (those affecting more than 5 percent of patients), linkage studies might do a better job of finding regions with many different, rarer mutations (affecting fewer than 1 percent). Since rare SNPs often confer a higher risk of disease, the linkage scan remains a powerful tool. The SNPs uncovered in the *Molecular Psychiatry* paper include a suspect region on chromosome 8, where a gene for neuregulin 1 is also found. The finding supports studies in mice showing that mutations in this gene lead to poorly developed neurons and a schizophrenia-like condition in what would be the mouse’s adolescence, tracking with the disorder’s time course in humans. Though the linkage study by Levinson and coworkers did not directly implicate the neuregulin 1 gene, the finding hinted at multiple problematic sites in that region, possibly providing a rationale for future studies to re-sequence this area, the authors wrote.

**From SNP to Brain Imaging**

The larger meta-analysis also turned up a possibility on chromosome 2, in an area associated with bipolar disorder and psychosis. A gene on this chromosome, dubbed ZNF8044, was tentatively implicated in schizophrenia in a 2008 *Nature Genetics* study. In 2009, a team of researchers reported in the May 1 issue of *Science* that they used a SNP in this gene as the basis of an imaging study to determine the SNP’s role.

Schizophrenia is increasingly seen as a disruption of the synchronicity between brain areas, not simply as a deficit in one area or neurotransmitter. To investigate whether the affected gene plays a role, Andreas Meyer-Lindenberg of the University of Heidelberg, along with colleagues at Heidelberg and the University of Bonn, studied 115 otherwise healthy subjects carrying the SNP in question. The researchers asked the subjects to perform tasks designed
to challenge two brain areas, the dorsolateral prefrontal cortex and hippocampus—both essential for complex thinking and memory, which are impaired in schizophrenia.

Using functional magnetic resonance imaging to monitor brain activity while the subjects performed the tasks, the researchers found that patients with the SNP showed reduced connectivity between these areas: the brain structures were working, just not coordinating. The authors suggested that future research should examine the role of ZNF8044 in the development of axons (projections along which neurons communicate) and in plasticity (the fine-tuning of connections between axons and neurons).

**Copy Number Variations**

Another discovery has opened up even more possibilities in understanding the genetics of psychiatric illness. This is a mutation called a copy number variation (CNV). If a SNP is a misspelling of a single letter of the genetic code, CNVs are analogous to whole groups of paragraphs being deleted, duplicated or shuffled.

Many brain disorders are known to result from deletions or duplications of chromosomes: Children born with Down’s syndrome, for example, have an extra copy of part or all of chromosome 21. Chromosomes—and extra chromosomes—can be seen with an ordinary microscope. CNVs, however, are deletions or duplications of stretches of nucleotides—often quite long—within a given chromosome. The first genome-wide description of CNVs was reported in 2004 by Stephen Scherer at the Hospital for Sick Children, Toronto, and his colleague Charles Lee at Harvard University, and concurrently by Michael Wigler at Cold Spring Harbor Laboratories, in New York State. Then a team led by Scherer published a “map” of CNVs in worldwide populations in the November 23, 2006, issue of *Nature*.

CNVs have been observed between identical twins who otherwise have the same genome. This fact may explain why, in many diseases such as schizophrenia, the twin of an afflicted individual has only a 50 percent chance of having the disease—presumably, with identical DNA, the odds should be 100 percent. Though rare, CNVs are powerful, conferring a high risk of disease. They are already proving informative when it comes to mental illness, Scherer
said. “CNVs seem to have a propensity for neuropsychiatric disorders—they’re involved in much higher proportions, and early data suggests they play a role in almost all psychiatric illnesses. You don’t yet see the same significance with other types of disease, although it is early days.”

**Cellular Suspects in Autism**

Among researchers, hopes are high that CNVs will shed new light on autism, which is not so much a distinct disorder as a common factor in many conditions and syndromes—some of which differ widely in other respects. Autism is increasingly described as any of a number of “autism spectrum disorders,” which can include impairments in social interaction and communication, repetitive behaviors, hypersensitivity to stimulation and onset before age 3.

Like SNPs, CNVs help to illuminate the process through which a disease unfolds. In the February 2008 issue of the *American Journal of Human Genetics*, Scherer’s group reported more than 200 CNVs in families with autism, some of them encompassing half a dozen genes involved in neural development but never thought to play a role in autism—as well as further implicating several genes already suspected.10

A study in the April 2009 *Molecular Psychiatry* used both SNP and CNV clues to pinpoint several genes that warrant further study.11 All are thought to be involved in the formation of synapses, the points of contact between neurons.

A child is born with far more neurons than he or she will end up with as an adult. Circuits in the brain are sculpted on the basis of the child’s experiences, with the density of synapses increasing in areas that are used—music, foreign language, sports, for example—and decreasing in those that are not. Synaptic formation and, eventually, “pruning” are normal stages for the developing brain. Autism, which usually appears between 18 months and 2 years of age, is thought to result from a disruption in this process. Too many or too few synapses are features in several syndromes that include autism.

Anthony Monaco of the Wellcome Trust Centre for Human Genetics at the University of Oxford joined with colleagues at 11 centers in the United States and Europe to examine areas on chromosomes 2 and 7, implicated in previous research. Drawing on techniques from both association and linkage studies, the researchers
checked for SNPs and CNVs of approximately 250 families, matched against 188 controls. The hot spots that turned up were compared with a European sample representing 300 afflicted families.

One gene of interest on chromosome 2, containing a SNP, was ZNF533. This gene encodes for several proteins that attach to DNA molecules and play a role in turning the gene on or off. Deletions in this gene have been found in patients with mental retardation.

The team found CNVs (deletions) spanning two genes on chromosome 7, called IMMP2L and DOCK4, which are prevalent in the fetal brain and active during neural development. A SNP, of the too few synapse commonality mentioned above, also turned up in DOCK4, which is thought to be involved in the growth of dendrites (the “receiving” points on neurons with which axons communicate).

“Taken together, these findings and others point to the synapse as a possible site for genetic effects of autism to occur,” said Monaco. He also believes that CNVs will eventually be diagnostic, adding that as microarrays become more sophisticated they are also getting cheaper.

Back-to-back studies in the April 28 Nature also pointed to pathways of brain development. Both were led by Hakon Hakonarson of
the Children’s Hospital of Philadelphia, turning up SNPs and CNVs encompassing genes involved in brain development. Some of the affected genes coded for cell adhesion molecules, which are important in order for developing neurons to reach their proper location in the brain.12,13 Others coded for ubiquitin, a neuronal protein that “tags” other proteins to be degraded and disposed of (a necessary step in brain development).

“The findings support imaging studies that suggest a lack of connectivity between brain regions involved in higher-order activities,” said coauthor Daniel Geschwind of the University of California, Los Angeles. “The variants seem to be in pathways involved in the brain’s wiring during development, but it’s not a done deal yet.”

Like Monaco, Geschwind is excited about the diagnostic possibilities suggested by both SNPs and CNVs. He added that between 5 and 10 percent of variants are “de novo” mutations, meaning they were not passed on by either parent. “If you can say for sure that your child has a de novo mutation, then subsequent children are at no higher risk than anyone else.”

**CNVs and Schizophrenia**

Some copy number variations now emerging are common to both schizophrenia and autism. A CNV on chromosome 15, for example, increases the risk of schizophrenia, autism, mental retardation and epilepsy.

At the National Institute of Mental Health, Anjene Addington and Judith Rapoport have discovered CNVs involved in childhood-onset schizophrenia, a rare form of the disorder in which symptoms appear before age twelve (onset in late adolescence is typical). Like other early-onset diseases, schizophrenia of this type is more severe. Working with a group of 150 patients with childhood-onset schizophrenia, followed by the NIMH for more than twenty years, the researchers replicated findings identifying four susceptibility genes in adult-onset schizophrenia and showed that the same four suspects were found in early-onset disease as well. Reasoning that these might confer especially high risk, the researchers looked for copy number variations in these genes.14 Four patients had a deletion on chromosome 22 that has previously been associated with autism, mental retardation and facial dysmophy. Two patients
showed a duplication in a region of chromosome 16 also found to be disrupted in adult schizophrenia in previous studies. Because two out of one hundred (2 percent) is a far greater rate than was found in adults, the researchers surmise that this CNV may confer exceptionally high risk.

The researchers found CNVs in three other genes involved in neural development and implicated in autism, adult schizophrenia or both. The authors wrote that if all the CNVs impacting the genes identified in their 105-patient group were disease-causing, they could explain the origins of schizophrenia in almost 40 percent of the patients. “This is a huge leap from where we stood just one or two years ago,” the authors wrote, adding that studies to re-sequence the target areas are under way.

**miRNAs Suppress the Code**

Some genes malfunction not because of any flaw in their construction, but because the information they encode is never brought into reality. Such alterations in a gene’s “expression,” rather than its DNA sequence, are increasingly described as “epigenetic” and represent a new way of understanding many kinds of illness, including psychiatric disorders.

A gene’s protein is produced in two steps. The first, transcription, occurs when the DNA code is synthesized into an intermediate molecule called messenger RNA (mRNA). The second step, translation, converts the mRNA into the sequence of amino acids (chemical building blocks) that make up the final protein “product.”

In recent years, small molecules called microRNAs (miRNAs) have been shown to influence translation, in normal processes as well as in disease. A better understanding of their actions may lead to better-targeted “gene silencing” therapies that prevent faulty genes from being translated.

miRNAs do not become translated into protein but attach themselves to other stretches of RNA that do—regulating the production of the gene’s protein and sometimes even “silencing” the gene. When acting normally, miRNAs elegantly help to control cellular processes. But miRNAs have also been implicated in many diseases, including heart disease and some cancers. Though they do not act on all genes everywhere in the body and brain, miRNAs are prevalent in the
prefrontal cortex (the seat of “higher” functions such as reasoning and analysis).

Schahram Akbarian, Nikolaos Mellios and colleagues at the University of Massachusetts Medical School have shown that in schizophrenia, a specific miRNA, designated miRNA 195, may upset the balance of brain chemicals. In a postmortem study of the prefrontal cortex of twenty subjects with schizophrenia and twenty controls, the researchers found that higher amounts of miRNA 195 led to reduced levels of two important messenger chemicals: gamma-aminobutyric acid (GABA) and a neuron-nourishing compound called brain-derived neurotrophic factor (BDNF). GABA is an “inhibitory” neurotransmitter that signals neurons to slow down their firing rate. Previous research had shown that this messenger is insufficient in schizophrenia.

“Many researchers believe that GABA acts as a kind of orchestra conductor to coordinate activity among brain areas,” Akbarian said.
“For this neurotransmitter to be disrupted may be like the conductor becoming distracted and the musicians playing chaotically.”

The finding by Akbarian and Mellios, reported in the June 15 *Biological Psychiatry*, revealed yet another level of complexity but also of specificity, suggesting that miRNA 195 contributes to the disease by reducing these two key chemical messengers.15 The study also points to miRNA 195 as a possible target for gene-silencing therapies still to be developed in the future, perhaps ushering in a day when schizophrenia could be treated by preventing certain genes from being translated into protein.

**Epigenetic Changes in Suicide**

Many psychiatric illnesses are assumed to result from one or more “susceptibility genes” that are set in motion by some trigger from the environment. But a striking study from McGill University, Montreal, showed just the opposite: environmental trauma in the form of child abuse can actually cause genetic changes—in ways that can lead to suicide.

Reporting in the March *Nature Neuroscience*,16 Michael Meaney and colleagues examined brain tissue taken postmortem from suicide victims with and without histories of childhood abuse, as well as control samples from individuals who had died suddenly of other causes. The researchers focused on the hippocampus, a part of the brain that plays a role in stress, emotion and memory. The hippocampus is studded with receptors for the stress hormones known as glucocorticoids, which play many roles in the stress response.

Glucocorticoid receptors have their own shutoff mechanism, keeping in balance the amount of stress hormones that enter the hippocampus. Some conditions like major depression and post-traumatic stress disorder involve a loss of neurons containing the receptors—which, paradoxically, can lead to high levels of stress hormones in the brain and a host of stress-related disorders.

When Meaney and colleagues examined the brain tissue of abused subjects who had committed suicide, the brains of child-abuse victims showed several differences. There were signs that glucocorticoid receptors had decreased in number; the genes encoding the receptors showed alterations in the “promoter” region where the process of gene expression begins; and activation of the promoter region...
occurred through a different type of chemical process. None of these changes were seen either in the brains of suicides who were not abused or in the controls.

The finding suggests that suicide can be considered a developmental disorder, in the sense that trauma in childhood causes biochemical changes and changes in gene expression that ultimately lead to the tragic event. “Our data are consistent with the hypothesis that early life events can alter the epigenetic state of relevant genomic regions, the expression of which may contribute to individual differences in the risk for psychopathology,” the authors wrote.

Looking Ahead

The explosion of research in the last few years will make it possible to scan the entire genomes of thousands, even tens of thousands of individuals. “The challenge will be to analyze the data and figure out what it all means,” said UCLA’s Geschwind. The genetic variants now showing up in multiple genes may map out different pathways of disease development that converge at one target site for future medications. This scenario is possible, though unlikely, Geschwind said. More probable is that subsets of psychiatric illnesses will be classified and understood according to their genetic basis and development.

Geschwind added that even though known genetic variants remain rare, still they add up. In autism, for example, the best-known variants affect only 0.5 to 1 percent of patients. “But if you can develop tests for several SNPs or CNVs at once, you might be able to explain 5 or even 10 percent of cases,” Geschwind said. “Since schizophrenia affects about one in 100 people, and autism about one in 150, the total number of patients and families is considerable.” A genome-wide scan might cost about $1,000, but Geschwind notes that routine tests such as CT scans and MRIs cost as much—with a similarly “low yield” of finding disease in 1 to 5 percent of patients. The same rationale holds true for neuropsychiatric illness, Geschwind said. The power of genetics will be of great benefit for the families coping with these disorders.
Two genetics studies in 2009 gave scientists a more nuanced understanding of Williams syndrome, a rare genetic disorder characterized by a curious collection of symptoms. Patients are mildly mentally retarded or have learning difficulties. They have good verbal skills and short-term memory, but have great difficulty with visuospatial tasks such as writing and drawing. Individuals with Williams syndrome have a distinctive appearance, including wide mouths, full lips and narrow chins; they tend to be short and have curvature of the spine. Finally, Williams syndrome patients are empathetic and gregarious, often maintaining too much eye contact and standing too close for other people’s comfort.

The condition is caused by a deleted area in chromosome 7 that spans about twenty-four to twenty-eight genes. A 2009 study by Julie Korenberg at the Brain Institute at the University of Utah teased out the genetic basis of the two “halves” of the disorder. Previous research had implicated two “transcription factor” genes that regulate other genes involved in brain and muscle development.

Reporting in the March *American Journal of Medical Genetics*, Korenberg and colleagues sifted through the genomes of seventeen Williams syndrome patients looking for individuals who had lost one gene or the other, but not both. The search yielded a girl who had retained one, named GTF21. The girl’s IQ, vocabulary, math and drawing skills were much closer to normal than those of other patients, and though outgoing, she did not show the hyper-social behavior characteristic of the disorder. She did, however, have the distinctive facial features characteristic of the disease. In maze and object-assembly tests, she scored lower than average for Williams syndrome patients.

The patient’s profile of strengths and weaknesses suggested that the gene she does have, GTF21, plays a role in social behavior, while the other, GTF21RD1, is involved in visual-spatial performance, the authors conclude.
Deep brain stimulation (DBS) involves neurosurgery to implant electrodes directly into specific brain regions. A battery pack is surgically inserted under the skin, usually in the chest, and wires link the battery pack to the electrodes, which deliver a continuous current of electricity to alter abnormal patterns of nerve activity. Newer DBS systems have longer-life batteries, which reduces the need for battery replacement, and programmable control packs that allow physicians—and sometimes patients themselves—to adjust the strength of the electrical current. (St. Jude Medical)
The year 2009 may be remembered as the beginning of a new era for deep brain stimulation, the neurosurgical therapy that uses implanted electrodes to alter brain activity. Backed by a promising track record in treating Parkinson’s disease and other movement disorders when all else fails, deep brain stimulation (DBS) has stepped solidly into the realm of psychiatry and is being investigated as a treatment for obsessive-compulsive disorder (OCD) and depression, along with a growing list of other experimental uses. These new experimental treatments underscore both the potential for using “neuromodulation” to treat a wide range of brain-based conditions and the pitfalls of the past that must be avoided.

Even as the field surges forward, many experts have urged caution in making the transition from research to clinical use of DBS in psychiatry. Editorialists writing about the expansion of DBS have frequently invoked the failed “psychosurgeries” of the mid-twentieth century, when Walter Freeman and his followers performed some 18,000 frontal lobotomies on patients with all manner of psychiatric and behavioral problems. “Given this checkered history of psychiatric neurosurgery,” wrote National Institute of Mental Health director Tom Insel and Wayne Goodman, now chairman of psychiatry at Mount Sinai Medical School, in a commentary in February, the scientific and medical communities “owe the public a promise that clinical applications of DBS in neuropsychiatry will not overstep the bounds of empirical evidence.”

To be sure, DBS is no “ice-pick lobotomy,” the technique Freeman championed. Modern neurosurgical techniques and brain imaging...
have made precise placement of minuscule electrodes into the brain a relatively safe procedure. But DBS is still neurosurgery, with all the inherent risks that surgery on the brain entails. Proponents of DBS often point out that, unlike ablative surgery, in which neurosurgeons lesion a discrete piece of the brain for therapeutic purposes, brain stimulation devices can be removed or regulated if necessary. Nevertheless, manipulating brain circuits with DBS can have unexpected side effects—good or bad—that may not be reversible even when stimulation is stopped.

**Spreading “Like Wildfire”**

While scientists continue to evaluate the dangers and ethical considerations, clinical use and research on brain stimulation as a therapy are exploding. “It has spread like wildfire,” said Mahlon DeLong, a pioneer of DBS for movement disorders at Emory University. A search for “deep brain stimulation” on PubMed, the public database of peer-reviewed journals, brings up nearly 4,000 articles—more than 250 in the last year alone, a substantial increase over the number five years ago.² Clinically, an estimated 60,000 patients worldwide, the vast majority of them with treatment-resistant Parkinson’s disease, have been treated with DBS.

Brain stimulation techniques have been used for more than fifty years as a treatment for chronic pain syndromes, and they are still used for this purpose in Europe (the FDA has not approved such procedures for pain in the United States). French neurosurgeon Alim-Louis Benabid pioneered the use of DBS in movement disorders in the 1980s, targeting a brain area called the thalamus on the basis of prior evidence that ablative surgery on the thalamus eliminated tremors. The brain target was subsequently refined after animal studies showed that lesions in the subthalamic nucleus dramatically reversed Parkinson’s-associated tremors. In addition to its use in Parkinson’s disease, DBS is currently FDA-approved for use in dystonia and essential tremor.

Only a small portion of DBS procedures—fewer than 150, as recorded in published reports—have been performed on patients with psychiatric conditions, but these disorders are the fastest-growing area of clinical research, judging by the number of clinical trials under way and the proliferation of published reports. In February 2009 the
U.S. Food and Drug Administration approved the first use of DBS for a psychiatric condition, issuing a “humanitarian exemption” to one device maker to allow treatment of severe, treatment-resistant obsessive-compulsive disorder (OCD). Meanwhile, researchers are conducting clinical trials to investigate DBS as a treatment for OCD, depression and Tourette’s syndrome, where promising preliminary results have encouraged further study. Clinical trials are also ongoing for the treatment of epilepsy.

An array of other experimental applications is just beginning to be explored, including obesity, brain injury, minimally conscious states, chronic pain, headache, Alzheimer’s disease, anorexia, tinnitus and addiction. And intriguing early research in animals has shown that brain stimulation can generate new nerve cell growth and improve cognitive skills, opening whole new avenues of potential clinical applications down the road.

In addition, research is also on the rise for neuromodulatory methods that do not require brain surgery, including transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS).

The premise for these techniques is the same as that for DBS: stimulating neural activity to modulate specific pathways. In tDCS, one or two sponge-tipped electrodes are placed on the surface of the scalp; in TMS, a magnetic coil of wire is placed over the head to generate magnetic fields within the brain that in turn cause neurons to fire. Both devices are non-invasive and can be applied in a physician’s office without requiring surgery. Neither technique is as precise as DBS, nor can the stimulatory effects reach more than a couple of centimeters into the brain, although an emerging technique known as “deep TMS” uses a novel coil design to modulate tissue deeper in the brain.

TMS is currently FDA-approved for treatment-resistant depression and is being investigated for a number of other neurologic and psychiatric disorders, including anxiety, schizophrenia and sleep disorders. An NIH-sponsored clinical trial in Parkinson’s disease is under way, with early results indicating that the technique is safe. An Israeli company, Brainsway, is investigating deep TMS for severe depression and several other conditions, including acute ischemic stroke. On its Web site, the company says the treatment may improve motor recovery after stroke by stimulating nerve growth factors that strengthen synaptic connections and may help generate
Transcranial DCS is in early stages of exploration for therapeutic use, with various research groups studying its potential for treating depression, schizophrenia, migraine, memory impairment and chronic pelvic pain, according to listings in the government’s Clinical Trials database.

Rhythms Gone Wrong

The broadening use of DBS and its non-invasive neuromodulatory cousins reflects not only technological advances but also a growing recognition that the symptoms of many brain disorders arise from disrupted circuitry—some aberration in the normal rhythm of brain signals—along the neural pathways that underlie the disordered behavior. (The term “circuit disorder,” also known as “dysrhythmia,” is increasingly being used to describe these conditions.)

In Parkinson’s disease, for example, a brain circuit linking the basal ganglia to the thalamus and cortex is disrupted, which causes tremors and other problems with movement (see chapter 3, “Parkinson’s
Disease”). Well-targeted stimulation within the circuit modifies the rhythm and has proven effective at quelling the motor symptoms of Parkinson’s in patients for whom no other therapy works. Current studies in OCD and depression are based on recent discoveries about the neuroanatomy of these disorders that implicate a circuit disruption as well.

“If one looks carefully across a range of neurologic and psychiatric conditions, one finds that a very similar neural mechanism—an abnormal brain rhythm—can generate many different types of symptoms depending on where in the brain that activity is,” said Rodolfo Llinas, a neuroscientist at NYU Medical Center. “This is absolutely why we are seeing such success with deep brain stimulation.”

**Why It Works: Knowns and Unknowns**

The mechanism of action of DBS is often said to be unknown, but Llinas scoffs at this notion: “People think you just stick electrodes in the brain and look for a sweet spot. They think we really don’t know how it works. That’s not true. We do know how it works. The only thing that electrical stimulation can do, especially acutely, is modify the rhythm.” Which rhythm is modified, and which neurons are stimulated, depends upon where the electrodes are implanted.

Beyond the general action of circuit modification, though, the precise way in which DBS works to mitigate debilitating symptoms that no other treatment can touch is “hotly debated,” according to Mount Sinai’s Goodman. More likely than not, it differs depending on the condition treated, the brain area targeted, the types of neurons activated and even the frequency or pulse rate of the electrical signal generated. In some cases, stimulation may return a disease-disrupted rhythm to a more normal pattern by activating or inhibiting select groups of neurons. In other cases, it may increase the firing rates of neurons in a given circuit or neutralize an aberrant pattern of nerve firing before it develops into, say, an epileptic seizure.

In addition, increasing evidence suggests that electrical stimulation acts to turn on certain genes that can cause downstream effects on cells, synapses and circuits. Some genes are activated immediately, while others are turned on after long-term stimulation. Researchers are only beginning to sort out how these gene expression dynamics relate to therapeutic responses. The array of genes affected depends
on whether the stimulation is applied continuously or only in the short
term, suggesting that long-term DBS may trigger secondary changes
as the ever-plastic brain adapts to new firing patterns. These effects—
and their behavioral consequences over time—are being investigated
in dozens of laboratories around the world.

Calming Compulsions: DBS for OCD

Brain stimulation for OCD, a chronic and debilitating illness that
affects 2 to 4 percent of people in the United States, has been studied
for more than a decade, and the FDA’s recent approval of its use in
severe cases marks the first psychiatric indication for DBS. Up to
4,000 people per year can be treated under the “humanitarian device
exemption” granted to Medtronic, the maker of the only DBS system
currently approved in the United States, though the company said in
a statement that it anticipated that the therapy would be appropriate
for only “a small subset” of the OCD patient population—those who
suffer the most severe debilitation and for whom no other treatment
provides relief.

The special regulatory status reflects both the high rates of treat-
ment failure in OCD—40 to 60 percent of patients don’t respond
fully, or at all, to current therapies—coupled with promising results
in preliminary studies. In one pilot clinical trial involving eight
patients that was funded by the NIMH and published in 2006,
researchers reported “promising long-term effects” in the group of
highly treatment-resistant patients, including a 35 percent decrease
in obsessive-compulsive symptoms and improvements in depression,
anxiety and quality-of-life measures. A second NIMH-sponsored
trial for patients with severe treatment-resistant OCD, led by
Benjamin Greenberg of Brown University/Butler Hospital, started
in March 2008. Unlike the pilot trial, the study includes a control
group of people who receive the implants but whose stimulators
are not turned on until three months into the study, an attempt
to better distinguish any placebo effect from true stimulation-
induced effects.

The brain target of stimulation in both studies is an area called
the ventral capsule/ventral striatum, which has long been implicated
in OCD, in part because surgical lesions in this area are known to
improve symptoms of the disorder. Goodman describes the area as
A “giant fan-like bundle of white-matter fibers that acts as a super-highway for nerve signals on their way to other brain regions.”

A separate study of DBS in severe treatment-resistant OCD, by the Paris-based STOC Study Group, stimulated nerve cells in the subthalamic nucleus, a brain region that integrates motor, cognitive and emotional components of behavior and that has long been a target of DBS for Parkinson’s. The results, published in the *New England Journal of Medicine* in late 2008, suggested some benefits in symptom reduction but also a substantial risk of serious adverse events among the sixteen people enrolled, raising concerns about the risk-benefit ratio of the treatment that experts say need to be explored further in well-designed trials.

**Tackling Severe Refractory Depression**

The application of DBS to severe depression has attracted considerable attention, in part because it is helping researchers delineate a “depression circuit” in the brain—or perhaps more precisely, a depression-relief circuit. Two large clinical trials and one smaller trial are ongoing with people who have severe treatment-refractory depression (TRD), for which virtually every antidepressant therapy has failed. Each study targets different brain areas. Medtronic is funding a Phase II safety and efficacy trial in 200 patients, following a pilot study led by Donald Malone of the Cleveland Clinic that demonstrated the safety of the approach in fifteen patients. The brain target is the same as the
ongoing trial in OCD—the ventral capsule/ventral striatum—and was selected in part because some patients in the OCD trial experienced improved mood after stimulation was applied to the area.

Meanwhile, St. Jude Medical, a would-be challenger to Medtronic’s domination of the U.S. DBS market, is supporting a clinical trial in one-hundred patients with TRD. The trial, led by Andres Lozano, a neurosurgeon at the University of Toronto, is based on previous clinical research by Lozano and Emory University’s Helen Mayberg that showed a response to treatment (defined as a 50 percent or greater decrease on a depression symptom scale) in about half of the twenty patients who received continuous stimulation for one year, including six who experienced complete remission of their depressive symptoms. The researchers have targeted the so-called “area 25” in the subgenual cingulate cortex, an area identified in a series of functional brain-imaging studies as being important to the resolution of depressive symptoms by various therapies.

Lastly, Thomas Schlaepfer of the University of Bonn is running a Medtronic-supported pilot study with twelve patients in which the nucleus accumbens is the brain region of interest, stemming from the accidental discovery during a trial for OCD that stimulating this area improved depression symptoms in study subjects.

So far, researchers have not discovered which of these competing targets may prove more useful in bringing relief in the most severe

Helen Mayberg of Emory University and Andres Lozano of the University of Toronto pioneered the use of deep brain stimulation to treat depression.
(Courtesy of Helen Mayberg / Emory University, Courtesy of Dr. Lozano / University of Toronto)
cases of depression. “The world experience is not that large yet,” said Dennis Charney, dean of the Mount Sinai School of Medicine. “The results so far are interesting because they do seem to implicate particular brain regions as important in the circuits of depression. There just needs to be a lot more work done to determine who it works in, what percentage sees improvement, and whether the response is maintained over time.”

**Epilepsy, Consciousness and Beyond**

Medtronic is also funding a randomized controlled trial in 110 patients with epilepsy at seventeen U.S. study sites, with the goal of obtaining “premarket approval” from the FDA for an epilepsy indication. Results have not been published in a peer-reviewed journal, but preliminary data presented at a scientific conference in December 2008 indicate that seizure activity was reduced by a median of 38 percent in patients—a significantly higher figure than the 15 percent in a control group whose stimulators were activated after a delay (all patients remained on their anti-epileptic medications). The brain target in this case is the anterior nucleus of the thalamus, a central “switching station” of the brain where neuronal messages are integrated and relayed on to other brain regions.

Smaller-scale studies are under way in severe intractable Tourette’s syndrome at several sites. Published reports have encompassed about thirty-five patients in total, with the largest study to date enrolling eighteen people and targeting a discrete region of the thalamus. Other studies are aiming at different brain targets. A Paris-based team is recruiting fourteen patients for a study in which stimulation is directed at the internal globus pallidus. Overall, the treatments have shown some encouraging success in controlling the debilitating tics that characterize the disorder, but no clear consensus has emerged on the best approach or which patients are more likely to benefit from DBS treatment.

Reports of completely novel applications of brain stimulation—many with only one or two subjects—are now trickling in from around the globe. At the University of Toronto, Lozano and colleagues have used DBS to treat obesity in a 420-pound man and observed, unexpectedly, that the stimulation evoked detailed autobiographical memories. While long-term weight loss was unsuccessful, the incidental finding
of memory recovery prompted the researchers to undertake a pilot study of DBS in six patients with early Alzheimer’s disease. A media report in June quoted Lozano as saying the treatment appeared to be “safe and promising.” Donald Whiting and Michael Oh at Allegheny General Hospital in Pennsylvania are pursuing the weight-loss application and have begun a three-patient FDA-approved trial to test whether tamping down neural activity in the lateral hypothalamus, the brain’s “feeding” center, can help obese subjects lose weight. Researchers from Milan, Italy, have reported some success in treating severe cluster headache, having followed about 18 patients for up to eight years.

In what has been called one of the most remarkable findings yet to emerge from DBS research, Nicholas Schiff and colleagues at Weill Cornell Medical have reported on a thirty-eight-year-old man who had been in a coma for six years and regained some cognitive and motor abilities following stimulation of the central thalamus, a brain area crucial to arousal and wakefulness. The man, who had suffered a severe brain injury, was described as being at the “higher end” of a minimally conscious state before the treatment, meaning that some level of awareness and environmental responsiveness had been preserved. While the work has attracted widespread media attention and raised hopes that comatose patients might be revived, Schiff has said that thalamic DBS does not appear to be useful for people who are in deeper comas. Weill Cornell, the Cleveland Clinic and JFK-Johnson Rehabilitation Institute in New Jersey are now collaborating to develop a strategy and uniform protocol to guide further investigations of DBS as a treatment for those in minimally conscious states.

The Challenge Ahead

As these and other clinical investigations for DBS therapy proceed—many of them unpublished and under the radar—numerous questions remain unanswered about how best to move forward with neuromodulatory therapies for brain disorders. It is not at all clear yet which brain regions are the best targets for treating a given disorder, what the most effective parameters for stimulatory frequencies and rates are, which patients are most likely to benefit or what the long-term consequences of brain stimulation are. Ethical quandaries also loom
large, as researchers feel their way forward in a complex, technically challenging field. Leading experts have consistently advocated for clear guidelines and “an abundance of caution,” as Goodman puts it, to try to ensure that the mistakes of the past are not repeated, particularly with regard to treatment of psychiatric disorders.

Nevertheless, with the right road map, attention to ethical standards and long-term follow-up of patients, neuromodulation in all its forms—including novel non-invasive methods that are just beginning to be explored—has the potential to change the way we think about and treat the worst of the worst in neurologic and psychiatric conditions.
A student in Dr. Tatsushi Toda’s lab at the Kobe University Graduate School of Medicine in Japan analyzes DNA in search of genetic variants that increase susceptibility to Parkinson’s disease.

(Courtesy of Tatsushi Toda / Kobe University Graduate School of Medicine)
Researchers are rethinking their approaches to studying Parkinson’s disease in hopes that a paradigm shift may inform new therapeutic targets and strategies. An important new direction for study addresses symptoms of the disease other than those resulting from the loss of the neurotransmitter dopamine.

Scientists have already discovered a wealth of information about what happens in the brain as Parkinson’s disease progresses, but very little of it has translated into effective treatments. In the past year, geneticists in Japan have uncovered several susceptibility genes for the disorder. Scientists at the Weill Cornell Medical College in New York have created what they believe is a superior animal model of Parkinson’s disease. And researchers at Harvard Medical School are bringing together data from epidemiological and evolutionary science work to investigate new treatments that may slow the disease’s progression.

What We Know—and Don’t Know

Parkinson’s disease is most easily described by its cardinal symptoms. These movement-related symptoms, including the telltale tremor, muscular rigidity, stooped posture and slowness of movement, were first described by James Parkinson in his 1817 article “An Essay on the Shaking Palsy.” Over the next two centuries, clinicians added to this early description associated effects of the disease such as sleep disturbances, depression, cognitive impairment and a variety of gastrointestinal problems.

These symptoms result primarily from the degeneration of a small but crucial group of dopamine-producing neurons in an area of the brain called the substantia nigra. When these cells die, the lack of dopamine release disrupts the synaptic functioning of the neurons in nearby areas, including the motor cortex and striatum. Parkinson’s disease is most often diagnosed when approximately 50–80 percent of these key substantia nigral neurons have been lost—and usually after symptoms are noticeable. But though scientists understand a great deal about this basic pathology, they are still unsure about just what causes the loss of these critical neurons.

Mahlon DeLong, an expert in Parkinson’s disease at Emory University, cites several mechanisms that could cause damage to dopamine neurons. “Mitochondrial dysfunction has been strongly
implicated,” he said, referring to the molecules that produce energy for cells’ activity, the mitochondria. “Oxidative stress, certainly, and the release of free radicals could result in the loss of these dopamine neurons. And others have considered protein aggregation. There’s certainly evidence that amassing an abnormal amount of a protein called alpha-synuclein plays an important role.”

Many people in the early stages of the disease can be successfully treated with the dopamine precursor drug levodopa (L-DOPA), which helps the brain replace enough dopamine to function successfully. But that treatment cannot be sustained indefinitely. Over time, with the loss of more substantia nigra neurons, the drug loses its ability to produce enough of this critical neurotransmitter. What’s more, despite the great inroads into understanding the underlying molecular pathology of the disease, scientists are now learning that Parkinson’s causes damage to more than just dopamine-producing neurons. Areas across the brain, spinal cord and peripheral nervous system are also affected, and their decline can lead to some of the more debilitating symptoms of Parkinson’s, such as sleep disorders, propensity for falls and cognitive impairment.

Simply put, scientists now know that Parkinson’s disease is more than just a dopamine deficiency. With this newer understanding, they are reexamining their theories about the neurobiological processes underlying Parkinson’s origins and progression in hopes of finding better treatments.
Genetic Susceptibilities

Part of the difficulty in understanding Parkinson’s disease is parsing both the genetic and the environmental components of susceptibility.

“About 5 to 10 percent of cases are familial,” said Tatsushi Toda, a genetic neurologist at the Kobe University Graduate School of Medicine in Japan. “A small portion of familial Parkinson’s disease is due to Mendelian inheritance, or a single-gene disorder. The rest of cases can be attributed to a multifactorial disorder comprised of what we presume are thirty to fifty susceptible genes mixed with environmental factors.”

Thus, the majority of cases of Parkinson’s disease arise from unknown causes or, as clinicians more commonly say, sporadic causes.

“It’s quite clear now that Parkinson’s is not a single disease,” DeLong said. “There are hereditary forms of the disease for which there are specific gene mutations that mean if you have the gene, you are almost certain to get it. There are cases where the disease seems to be due to environmental factors like toxins. But the vast majority of patients, we just don’t know what combination of genes and environmental factors may be at play.”

In addition, DeLong noted, atypical forms of the disease occur. Often referred to as Parkinson’s-like disorders, these include essential tremor, dementia with Lewy bodies, progressive supranuclear palsy and multiple system atrophy. DeLong and others have proposed that all of these disorders may be related, or even simply different points on a wide clinical spectrum of disease.

“It’s important to study all of these because we may find common mechanisms or pathways that these diseases share. Each of these disorders may start at a different point or have different chemical or biologic systems involved, but there may still be enough potential overlap to inform other areas,” he said.

“For example, the same gene transmitted in a family can appear as an essential tremor in some individuals and as Parkinson’s in others. That must mean that the genetic backdrop in those two family members is different enough that the gene is expressed differently. And understanding just how it is expressed differently may tell us quite a bit.”

These overlaps are driving current investigations of the genes responsible for Parkinson’s neurodegenerative effects. For example, for both Parkinson’s disease and the Parkinson’s-like dementia with
Lewy bodies, researchers have found a strong association with the glucocerebrosidase (GBA) gene, a gene linked to Gaucher disease, a disorder of the body’s storage of fatty acids. Parkinson’s-like dementia with Lewy bodies is a common form of dementia characterized by the buildup of alpha-synuclein protein in neurons in the motor and memory areas of the brain and accompanied by visual hallucinations.\(^2\)

In the May 2009 issue of *Archives of Neurology*, Toda and his colleagues demonstrated that individuals who had specific mutations of GBA were nearly thirty times more likely to develop Parkinson’s disease. In addition, individuals with these genetic variants were more likely to develop Parkinson’s at a younger age. A second study in the same issue, led by Columbia University’s Karen Marder, found an association between a mutated GBA gene and dementia with Lewy bodies.\(^3\) Since the biological changes caused by Gaucher, a single-gene disease, are fairly well documented, Toda believes that this association can provide new pathways and molecular mechanisms for researchers to examine these other disorders. It may be that doing so will provide new targets for drug therapies.

**And a Dash of Environment**

Other research has focused on environmental aspects. Parkinson’s disease has much higher incidence rates in industrialized countries and has been linked to a variety of external influences. For example, some clinicians hypothesize that boxers may be more likely to develop Parkinson’s disease from repeated blows to the head during their fighting careers.

In addition, excess iron exposure, cocaine use, exposure to pesticides and use of antidepressant medications have all been implicated in industrialized nations as possible triggers. But scientists do not know how these substances interact with one’s genetic makeup to increase susceptibility to the disease later in life, sometimes even decades after exposure.

“Parkinson’s is made up of much more than just our genes,” said DeLong. “Certainly there is a lot of evidence now that pesticides play some role in the development of the disease.”

Though epidemiological data have linked exposure to pesticides such as paraquat and beta-hexachlorocyclohexane (beta-HCH) to a higher risk of developing Parkinson’s, the exact mechanisms
underlying the neuropathology are still under investigation, the results of which scientists hope will shed light on other etiologies.\textsuperscript{4,5}

\section*{The Right Kind of Animal Model}

When it comes to finding potential treatments, clinical neuroscientists are utterly dependent on good animal models to test their theories. But to date, a truly analogous Parkinson’s disease animal model has not been developed. Part of that stems from the fact that Parkinson’s has such potentially varied origins. Single gene knock-out models—animals bred to have a specific gene missing—have proven useful in offering new treatment directions for diseases such as diabetes and cancer but, to date, no single model has been able to capture all of Parkinson’s tell-tale symptoms.

In the July 2009 issue of \textit{Nature Neuroscience}, Chenjian Li of Weill Cornell Medical College, introduced a new animal model, a LRRK2 transgenic mouse, that he argues is a more valid model for the human disease.\textsuperscript{6,7}

LRRK2 has been implicated as a gene of interest in the development of Parkinson’s disease in dozens of studies. And Li’s group mutated it in such a way that it overexpressed its related protein, leading to a model that demonstrates Parkinson’s most common symptoms for the first time.

“It’s been difficult to get really good animal models that really mimic the disease,” said M. Flint Beal, a neurologist also at the Weill Cornell Medical College and a coauthor on the paper. In particular, he notes, previous models have not shown the typical Parkinson’s phenotype including symptoms like slowness of movement or defects in dopamine release.

“We were able to create a unique model of Parkinson’s disease,” says Li. “Not only does it show an age-dependent motor deficit like you see in human Parkinson’s but that deficit can be rescued with levodopa treatment – something you also see in the human form of the disease. Plus, you also see dopamine transmission problems as well as axonal degeneration in the dopaminergic system.” Li states that though it is not a perfect replica of the human disease, it is a big step forward from previous genetic models.

And why is a better model so important? Beal believes that models that better imitate typical Parkinson’s disease may offer us a clean
slate of sorts. Previous pathways of interest or potential therapies that failed to yield results in animal trials may have done so not because they were wrong but because the model was not comparable enough to the human disease.

“With better models, we can go back and try again,” Beal says. “This is a superior model based on a known genetic defect in Parkinson’s. It really gives us a powerful tool to investigate potential therapies.”

Li agrees and takes it a step further. “When you have a good model, it’s almost as if you are setting up a stage. And on that stage you can perform different shows,” he says. “On one side, we can use a model like this to understand all the details of the mechanisms underlying the disease pathogenesis. But it is also a good stage for testing drug candidates. With the right models, we have the potential to serve both the scientific understanding and the pharmacological development sides of things.”

Michael Schwarzschild, a Parkinson’s researcher at Harvard Medical School, also thinks that there is value in newer, better animal models. “A good model is one that predicts the disease and things that will treat the disease. And, as we’ve learned, you don’t know whether it’s really predictive until you go to a human clinical trial,” he said. “It’s good that we are questioning old models and thinking about how to create better ones. They may offer us some good bets for potential human treatments down the line.”
some researchers hypothesize that oxidative stress, or the accumula-
tion of destructive free radical molecules due to an imbalance in the
brain’s oxygen levels, may trigger specific cellular processes that result
in the development of Parkinson’s disease. The clumping of a protein
called alpha-synuclein in memory and motor areas of the brain;
malfunction in neurons’ energy-producing apparatus, the mitochon-
dria; and good old-fashioned inflammation have all been implicated
in the death of dopamine-producing neurons. And scientists suspect
that these three activities may be somehow related. Though the
mechanism that connects them is, as yet, unknown, many suggest
that oxidative stress may be the process that triggers it, and as such,
sporadic Parkinson’s progression.

“Oxidative damage [the damage to neurons from oxidative stress]
is such a prominent mechanism for brain cell degeneration. You see it
in Alzheimer’s, Parkinson’s and other neurodegenerative disorders,”
said Schwarzschild. “So it makes sense that an antioxidant may help
in slowing the progression of the disease.” And one such antioxidant
of interest is the purine urate. Purines are basic nitrogen-containing
compounds that provide building blocks for many other signifi-
cant biological substances. For example, DNA and RNA contain
the nucleobases adenine and guanine, both of which are purines.
Urate is another member of the purine family—the end result of
purine metabolism in the body—and is believed to work as an anti-
oxidant, combating the effects of oxidative stress on cells throughout
the body.

Schwarzschild collaborated with Harvard School of Public Health’s
Alberto Ascherio after seeing the epidemiologist’s work identi-
fying urate as a predictor of whether an individual would develop
Parkinson’s disease later in life.

“Our clues have come about somewhat uniquely by working at the
interface of basic science and epidemiology,” he said. “Ascherio and
his colleagues linked urate to a reduced risk of getting Parkinson’s
disease. And so we wondered if somehow these compounds
were neuroprotective.”

Schwarzschild’s curiosity about urate was also fueled by some
interesting evolutionary data: humans and apes are missing the gene
that breaks down urate in the body.
Michael Schwarzschild of Harvard Medical School collaborated with Albert Ascherio of the Harvard School of Public Health to determine whether the concentration of urate in the blood predicts the likelihood of developing Parkinson’s disease. After baseline urate levels were calculated, participants in the study were tested over a period of two years. The end point was clinical disability sufficient to require dopaminergic therapy. In both men and women who went on to develop PD, participants with higher levels of urate approached the end point at a slower rate than those with a lower level of urate. (Copyright American Medical Association, Archives of Neurology. 2008 65(6):720.)
“Multiple mutations in this gene appear to have taken place millions of years ago in separate lines of primate evolution suggesting there was some selective advantage to having higher levels of urate circulating in human ancestors. Maybe it’s because urate can play a protective role in our bodies including our brains,” he said.

In the June 2008 Archives of Neurology, Schwarzschild et al. looked at the urate levels in 804 individuals with early-stage Parkinson’s disease. The results were striking.

“We found that individuals with higher rates of urate are not only less likely to develop Parkinson’s but, if they do get the disease, show slower rates of clinical progression,” said Schwarzschild. “This molecule might not only be useful to help predict who will get the disease but also who will do better with the disease if they already have it.”

Although Schwarzschild cautions that the association found does not imply causality, he hypothesizes that urate protects the dopamine neurons in the substantia nigra by preventing further oxidative damage. He and his colleagues are now in the beginning stages of a human clinical trial to elevate urate levels in Parkinson’s patients to see whether it improves disease outcomes.

Healthy vitamin D levels have also been linked to lower rates of Parkinson’s. Vitamin D had already been shown to have an anti-inflammatory effect in conditions from cancer to heart disease. Back in 2007, researchers at the Susan Lehman Cullman Laboratory for Cancer Research at Rutgers University hypothesized that vitamin D deficiencies played a role in the prevalence of Parkinson’s. And subsequent epidemiological data now suggest that they may be right.

DeLong and colleagues at Emory University compared vitamin D levels in patients with Parkinson’s disease, those with Alzheimer’s disease and individuals who were healthy in a study published in the October 2008 issue of Archives of Neurology. The researchers showed that vitamin D levels were not only significantly lower in Parkinson’s patients than in the healthy group but also lower than in patients with Alzheimer’s disease. DeLong warns that the data are preliminary and that there’s still a lot to understand about the role of vitamin D, but he plans to look at the clinical effects of vitamin D and Parkinson’s disease.

“Vitamin D is one of those neglected areas,” said DeLong. “We’re now doing a trial to see if treating the patient’s vitamin D deficiency has any effect on the symptoms or the progression of the disease.”
New Directions From Paradigm Shifts

Although the majority of Parkinson’s researchers are seeking the causes of neuronal degeneration, Bryce Vissel and his colleagues at the Garvan Institute in Sydney, Australia, are focusing their efforts on neurogenesis (see chapter 6, “Neuroprotection”).

“We have a perception that we clearly understand the fundamental underlying pathology of Parkinson’s—and that’s the loss of those dopamine nerve cells,” Vissel said. “But perhaps it’s not the loss of the cells that is as important as an inability to regenerate them.”

Vissel argues that the fact that an exposure to a toxin may cause Parkinson’s disease ten to fifteen years later in life gives us a mystery to be solved. It may be that Parkinson’s triggers an immune inflammation response that contributes to cell death and then prevents nerve cell regeneration.

In a study published in the June 2009 issue of *Stem Cells*, Vissel and his collaborators demonstrated in an animal model that the brain releases a chemical called activin A that helps to repair brain cells after damage due to injection of kainic acid, an excitotoxic chemical that causes a toxic glutamate cascade and, as such, widespread cell damage and death. This natural neuron regenerator works by inhibiting inflammation. Vissel argues that a better understanding of this natural neural repair process may help direct scientists to novel treatments that may prevent or slow the progression of Parkinson’s disease.

But it may also help to look beyond the neurons to better understand neuronal regeneration. Yuet Wai Kan from the University of California, San Francisco and Richard Smeyne from St. Jude Children’s Research Hospital in Memphis, Tennessee, have found evidence that a chemical released by astrocytes, a type of supportive glial cell in the brain, called Nrf2, may protect neurons from Parkinsonian neurodegeneration. When oxidative stress causes inflammation in the brain, the astrocytes attempt to mitigate it by releasing Nrf2. Glial cells may also provide researchers with new directions for Parkinson’s treatment.

The Best Treatments

Individuals in the early stages of Parkinson’s disease are most commonly treated with dopamine agonist drugs—that is, drugs that
stimulate the same receptors as dopamine itself—and have the benefit of postponing levodopa therapy, which can cause some troubling side effects. Anecdotal evidence has suggested that these dopamine agonist drugs may cause compulsive gambling and hypersexuality in some patients, and recent work is suggesting that the problem may be more widespread than initially thought.

In a study published in the April 2009 issue of Mayo Clinic Proceedings, J. Michael Bostwick and colleagues examined patients in the clinic’s large patient database to see how common these side effects were. After looking at the data on nearly three hundred Parkinson’s patients, they found that 18.4 percent of those taking dopamine agonist drugs alone were experiencing compulsive gambling and hypersexuality, some to the point that doctors were treating the patients as if they had a separate psychiatric disorder. The same effects were not seen in those patients who were prescribed different drug therapies for their Parkinson’s disease. Even more telling, once the drug therapy was stopped in these patients, the behaviors abated.

“There are so many areas in the brain that are directly affected by dopamine,” said DeLong. “And we’re only now becoming aware that these kinds of drugs are causing these very severe, very debilitating effects. These patients will gamble away their savings, their houses, and they manage to keep it all very secret. Doctors need to be more aware of these possibilities and really keep an eye on how their patients are doing when on these drugs.”

In the past few years, deep brain stimulation (DBS), a procedure that involves an implanted device delivering steady electrical current to the brain, has made headlines for its treatment of advanced Parkinson’s disease (see chapter 2, “Deep Brain Stimulation”).

Thus far, however, the risks involved with such an invasive treatment have caused several clinicians to choose to treat older patients with drugs instead of DBS. Some question whether the benefits would outweigh the risks in patients older than age seventy.

But Frances Weaver, a physician at the Hines Veterans Administration Hospital in Illinois, and her colleagues compared the efficacy of DBS versus medical therapies in both younger and older patients. In a study published in the January 7, 2009, issue of the Journal of the American Medical Association, the group found that patients treated with DBS had better outcomes in both motor function and quality of life six months after treatment.
On the other hand, they also found a small decrease in neurocognitive function in the DBS group and a higher incidence of adverse effects such as infections. Nevertheless, the researchers concluded that DBS was a more effective treatment for Parkinson’s symptoms than the most common medical therapies.

It is becoming more apparent that a true understanding of Parkinson’s requires more than just the study of dopamine deficiency. And with paradigm shifts offering new directions in the study of the disease’s etiology, most clinicians still share the same goal—to find ways to slow the progression of the disease. DeLong emphasizes that Parkinson’s treatment requires many new and better therapies to offer true relief to patients.

“The disease is more than just its cardinal, core features,” said DeLong. “Its fellow travelers play a huge role: the difficulty swallowing, the drooling, the mood disturbances, the autonomic nervous system impairment, the GI problems. Treating Parkinson’s means treating all of these. And to address them all comprehensively, we need to treat the mechanism underlying them all and treat not the symptoms but the disease progression.”
MRI scans of the brain of a person with relapsing-remitting multiple sclerosis taken at monthly intervals. The bright spots indicate active lesions, or locations where neurons have been stripped of their protective myelin sheath. (U.S. Brookhaven National Laboratory).
By using computers to compare thousands of genomes, scientists are identifying genes that occur more frequently among people with multiple sclerosis. This new knowledge about the genetic underpinnings of the disease supports the hypothesis that malfunctions of the immune system drive the disease, and suggests more effective strategies for treating it.

At present, almost all treatment options involve suppressing the most conspicuous consequence of the disease—the inflammation that damages myelin, the fatty white coating that insulates the slender fibers known as axons that transmit electrochemical signals away from a neuron’s cell body.

The multiple layers of myelin wrapped tightly around an axon enable signals to travel rapidly, producing movement, sensation, perception and thought. When damaged by inflammation, the myelin sheath develops a lesion or scar that disrupts those signals. Since the myelin of any axon in the brain and the spinal cord is vulnerable to attack, people with MS can develop a wide array of symptoms, among them numbness and tingling, vision loss, weakness, paralysis, tremors, poor balance, bladder and bowel problems and cognitive changes such as memory loss, poor concentration or difficulty in planning tasks.

The disease also varies greatly in severity. Some people have mild symptoms that occur rarely, and may cease altogether, while others progress to profound disability that prevents them from walking, feeding themselves and performing other routine tasks.

New genetic insights that reveal what makes some people more vulnerable to MS will undoubtedly help scientists treat the inflammation of the myelin that causes symptoms, and may also help them interrupt the disease before the inflammation causes problems.

Faulty Immune System May Be Tied to Genes

Axons in the brain and spinal cord, which constitute the central nervous system, or CNS, are protected by the blood-brain barrier, a tight layer of cells within blood vessels that prevents many substances from passing into the CNS from the blood, while allowing oxygen, glucose, other nutrients and a limited number of other substances to pass freely. Certain immune cells (T cells), which recognize and attack non-body molecules, are also blocked. In MS patients, however, these
cells somehow get through the blood-brain barrier and attack the myelin as though it were a foreign substance. This attack triggers the inflammation that damages the myelin sheath. Cells known as oligodendrocytes produce new myelin and wrap it around the newly denuded portions of axons, but this process is imperfect, and signals have difficulty crossing the patched areas. Eventually, the inflammation and residual demyelination and axonal damage results in cumulative and debilitating deficits.

About half a million people in the United States have MS, which usually appears in young adulthood as the relapsing-remitting form of the disease. During a relapse or exacerbation, the patient develops a symptom—numbness and tingling in an arm, perhaps, or loss of vision, or vertigo—which usually improves gradually, with or without treatment.

About 10 to 20 percent of MS patients, however, begin with primary-progressive MS, which involves a continuous, gradual decline in physical abilities.

About half of the patients who begin with relapsing-remitting MS progress within ten years to secondary-progressive MS, characterized

Four patterns seen in the development of multiple sclerosis.

(Wikimedia Commons, licensed under the GNU Free Documentation License)
by frequent exacerbations that produce severe symptoms resulting in permanent disability.

And a few patients—less than 5 percent—display a combination of the relapsing-remitting and primary-progressive forms of MS. They experience a continuous gradual decline punctuated by severe exacerbations that accelerate disability.

Circumstantial evidence strongly suggests that genes confer susceptibility to MS: The disease is most common among people of Northern European ancestry, while other groups, including European Gypsies, Eskimos and African Bantu, rarely get MS. Also, if one identical twin gets MS, the other has a 30 percent chance of getting it too, whereas the fraternal twin of an MS patient acquires the disease only 4 percent of the time. MS occurs more frequently among family members of people who have it, and women get MS three times as often as men. All these statistics make a persuasive case for a genetic model of illness.

However, an environmental trigger such as a virus is believed to initiate the disease in people who are genetically susceptible to it.

Most existing treatments for MS attempt to adjust the immune system in some way so it won’t attack myelin, but insight into the genetic underpinnings of the disease may lead to methods of preventing immune cells from getting into the CNS in the first place—a treatment that would effectively halt the disease process.

**Genome Studies Provide Clues**

The mapping of the human genome, combined with the massive computer power needed to analyze the DNA of vast numbers of people, is revealing subtle genetic differences among people with MS.

One ongoing study, for example, involves comparing the genomes of 22,000 people to find genes that occur more frequently in people with MS.¹

So far only a few genes have been found that appear to make people more susceptible to MS, with each gene contributing slightly to overall susceptibility. This evidence makes scientists suspect that MS, like diabetes, autism and other genetically complex diseases, involves many genes working together. “There will certainly be a hundred genes, maybe more, that are serious players,” said Stephen L. Hauser
of the University of California, San Francisco, who has created a DNA bank containing samples from MS patients and their relatives.

No single gene is likely to emerge as a major culprit, he added. “But I’m confident that genetic variants will lead us to novel pathways that will simplify our understanding of the disease and make a critical connection with environmental risk.”

The genetic findings so far support the prevailing theory that MS results when the immune system mistakenly attacks the myelin around axons.

“We now have about a dozen genes that have been implicated in MS, and they’re all immune genes,” said David A. Hafler of Harvard Medical School and Brigham and Women’s Hospital in Boston. “All are involved in dictating the immune response, and they all have incredible similarities genetically. Right now the genetics are explaining only a small part of the risk, and there are probably hundreds of variants working together, as in all complex genetic diseases, but we’re in the early stages. I think this is a very exciting time.”

Hafler expects a better genetic understanding of the disease to explain the wide variability in the severity of symptoms that MS patients experience. This also will allow for customized treatments that consider each patient’s unique genetic endowment.

“Now patients undergo a process of trial and error to find the treatment that works best for them,” he said.

Still, the genetic evidence so far fails to settle a fundamental debate regarding the cause of MS: Is the immune system attack on the myelin the cause of the disease or the result of another form of dysfunction elsewhere in the brain and spinal cord?

**Environment Leads to Inflammation**

“We don’t know the cause of MS—that’s the bottom line,” said Richard A. Rudick, director of the Cleveland Clinic Mellen Center for Multiple Sclerosis Treatment and Research. “And I think the two ideas about the disease are somewhat irreconcilable.”

The leading hypothesis maintains that an environmental trigger such as a virus causes the immune system to overreact and mistakenly initiate a persistent attack on myelin. (The Epstein-Barr virus, which causes infectious mononucleosis, is a leading contender.) The resulting scar or lesion in the myelin disrupts the transmission of signals and eventually
damages the neuron, producing the degeneration and permanent disability that appear in later stages of the disease.

The competing hypothesis asserts that the immune attack may be an appropriate response to defective myelin that is deteriorating for some reason and must be broken down and removed. In this model, the damage to the myelin results from an abnormality in the oligodendrocytes, the cells that produce myelin, or from dysfunction in the body of the neurons themselves, which supply the neurotransmitters that travel to the end of the axon and enable signals to jump from one neuron to the next.4

“In this hypothesis the immune system is responding to an abnormality, but also contributing to tissue injury,” said Rudick. “In this scenario, interrupting the inflammatory process might be partially effective, but it wouldn’t stop the underlying degenerative process.”

An Australian group led by John Prineas provided support for this idea with a 2004 paper that described the death of oligodendrocytes in MS lesions prior to any evidence of inflammation.5 Prineas argued that oligodendrocytes become sick before damage to the myelin appears.

While this idea has started to lose ground in the face of new genetic evidence that implicates immune dysfunction, MS clearly begins long before inflammation of myelin starts to cause symptoms. The widespread use of magnetic resonance imaging in recent years has found people who have “silent” MS lesions—damage that has never caused symptoms—and studies have confirmed that the loss of brain tissue in MS patients starts early in the disease process, even though neurological deficits don’t start to appear until years later.
“It seems as if patients compensate for considerable amounts of brain injury, but only up to a point,” Rudick said. “When they get past that point they start to deteriorate, and the disease looks more like a classic progressive neurodegenerative process. So there’s some evidence that the process underlying the disease changes from mostly inflammatory in the early stages to mostly degenerative in later stages of the disease.”

Finding New Ways to Modulate the Immune System

Even if the inflammation of myelin—the hallmark of MS—turns out to be a consequence of dysfunction in neurons or oligodendrocytes, suppressing the inflammation clearly helps control symptoms, and that’s what existing treatments as well as most new medications in the pipeline attempt to do.

Drugs such as interferon beta-1b (Betaseron), interferon beta-1a (Avonex, Rebif), along with glatiramer acetate, a synthetic product sold as Copaxone, interfere with the inflammatory hormones called interferons, substances produced by cells in response to viral infections. Known as immunomodulators, these drugs are believed to

Macrophages, or immune cells, stained brown here, crowd around a demyelinating MS-lesion.

(Wikimedia Commons, licensed under the GNU Free Documentation License.)
discourage T cells in the immune system from attacking myelin. They reduce relapses or exacerbations, as well as new lesions in the myelin, by up to one third, and their long history of use has shown them to be very safe. Patients may respond better to one drug than to others because of their unique genetic makeup, “but thus far we don’t have a way to individualize treatment,” said Rudick.

Several oral medications now in the pipeline are expected to be approved shortly, including cladribine (Leustatin), fingolimod, teriflunomide and laquinimod. Like drugs given to transplant patients to prevent rejection, these drugs suppress the immune system and thereby weaken its ability to attack the myelin of MS patients. While these drugs work primarily by destroying immune cells, fingolimod, also known as FTY-720, suppresses the immune system by confining lymphocytes to lymph nodes, thereby muting their ability to trigger inflammation.

Another drug recently approved by the FDA, natalizumab, is a highly specific type of antibody known as a monoclonal antibody. Administered every twenty-eight days, natalizumab acts on the walls of the blood-brain barrier to block inflammatory cells in the immune system from crossing into the central nervous system. It is also used to treat Crohn’s disease, a severe immune-mediated inflammation of the lining of the intestines.

Sold under the brand name Tysabri, natalizumab aroused high hopes when it was approved by the FDA in 2004 because it appeared to work nearly twice as well as existing drugs in preventing relapses and new lesions in MS patients. However, it was temporarily withdrawn from the market when three people taking it developed progressive multifocal leukoencephalopathy, or PML, a disease much like MS that causes inflammation in the myelin of the brain. Normally seen only in people with weakened immune systems, such as AIDS patients or those taking immunosuppressive drugs to prevent rejection of a transplanted organ, PML usually causes death. After a study, the FDA allowed natalizumab to return to the market in 2006. Since then about ten patients out of more than 40,000 who have taken it have developed PML, but none have died.

“The good news is that neurologists can recognize PML early,” said Peter Calabresi, director of the Johns Hopkins Multiple Sclerosis Center. “You can wash the Tysabri [natalizumab] out with leukopheresis and most patients do not die from PML. Even if we must use non-specific immunosuppressive drugs [on MS patients], the
drugs that are reversible are much more appealing than ones that have sustained effects.”

But PML is not the only serious complication of natalizumab, according to Joseph Berger, chairman of the department of neurology at the University of Kentucky College of Medicine.

“For instance, there’s also an increased risk of herpes infections,” said Berger, who addressed the May 2009 convention of the Consortium of MS Centers on the risk/benefit considerations of MS therapies. “What we typically see are recrudescences [revivals] of latent infections. Eighty percent of us carry JC virus, the cause of PML, yet PML is a vanishingly rare disease in the absence of an immunosuppressive condition or the administration of an immunosuppressant drug. The risk for developing infectious complications will likely be increased with many of these drugs being developed for MS besides natalizumab. As the efficacy of a therapy improves, the risks associated with it will increase as well.”

Nevertheless, by preventing immune cells from crossing the blood-brain barrier, natalizumab could conceivably slow or even halt the progression of symptoms if it is administered early in the course of the disease. However, because of the heavy side effects, neurologists tend to reserve the drug for those patients with the most severe disease, who have failed to respond well to all other treatments.

“If you put patients from the beginning of the disease on Tysabri and stop inflammatory lesions, do you stop the disease?” said Bruce D. Trapp, chairman of the department of neurosciences at the Cleveland Clinic Lerner Research Institute. “That is an experiment I would like to see. It could determine if the inflammation is primary or secondary.”

Trapp was the lead author of a 1998 article in the *New England Journal of Medicine* that transformed thinking about MS, which up to that time was thought to affect only myelin. He showed that MS also damages the nerve fibers themselves, which probably accounts for the severe long-term disability that afflicts some patients.

This conception of MS suggests that discovering how to protect the delicate nerve fibers and promote the body’s own efforts to repair myelin might be an effective way to stave off or even halt the degeneration that produces disability in MS patients. However, the development of such therapies is hindered by the lack of a technique to detect myelin non-invasively and thereby determine the effectiveness of such treatments.
“The best MS imaging labs in the world are working on this,” Trapp said, “but as of now we have no way of measuring an effective repair.”

In a paper published in the *Journal of Neuroscience* in 2009, however, Trapp and his colleagues reported the existence of a previously unidentified type of cell in the brain that gives rise to oligodendrocytes, which restore myelin that has been damaged by inflammation.6

“We developed a method to purify this cell, and we showed in a mouse model that fails to make myelin that it has a significant ability to generate oligodendrocytes,” Trapp said. “If we transplant the same number of these cells as we transplant progenitor cells, we get more myelination, suggesting that the repair capacity of this cell may be greater than that of an oligodendrocyte progenitor cell.”

**Stem Cells Provide Blank Slate**

A team at Northwestern University’s Feinberg School of Medicine, led by Dr. Richard Burt, has been “resetting” the immune system of MS patients by transplanting their own immune stem cells.7

In one study, eighteen of twenty-one MS patients with the relapsing-remitting form of the disease improved significantly for
twenty-four months after the stem cell transplant, and none got worse. Most patients with relapsing-remitting MS get progressively worse as irreversible damage to their neurons accumulates.

The procedure involves harvesting immune stem cells from the patient’s bone marrow, and then destroying the immune component of the bone marrow with chemotherapy. When the stem cells are transplanted, the patient develops a new immune system apparently free of disease.

“The stem cells are not immune cells,” Burt said. “They have to be educated. They have to differentiate and grow into immune cells. The reset [after transplantation] results in an immune system like a newborn child’s.”

Burt has applied this technique to other diseases, including type 1 diabetes, lupus, scleroderma, Crohn’s, and a form of vision loss known as autoimmune-related retinopathy and optic neuropathy syndrome, or ARRON.

Fixing Faulty Immune System Remains a Tough Challenge

What will the treatment of MS look like in the years ahead?

A deeper understanding of MS will almost certainly lead to the creation of a subspecialty within neurology dedicated to the treatment of the disease. “Management of patients with MS will become increasingly complex in the next five to ten years,” said Berger. “While neurologists will always make the diagnosis of MS, the treatment may become sufficiently complex that the average neurologist will defer to a specialist or a specialty group for the management of the MS patient. That’s where I see it going with the panoply of drugs likely to make it to market. I would also predict that genetic analysis of these individuals will enable us to predict who is going to respond to those therapies that are less aggressive.”

And if the past decade is any indication, the years ahead will bring much more effective treatments, according to Trapp.

“I don’t see a cure until we know the cause, and we don’t know the cause,” he said. “But we are making strides. What we’ve accomplished in the last ten years has been remarkable. The existing therapies, while not perfect, make a real difference in quality of life of MS patients.”
Researchers identified neurons involved in storing a specific fear memory by using the protein cyclic-AMP response-element-binding protein (CREB), highlighted green in this image, as a marker. Neurons recruited to form auditory fear memories have high levels of the protein.

(Courtesy of Sheena Josselyn / University of Toronto)
During the past several decades, researchers have worked toward a more detailed understanding of the brain structures that support memory. Their quest has revealed several of the components that control the storage of memories in brain circuits. Research in 2009 emphasized the molecular underpinnings that play a critical role.

One effort highlighted how the enzyme PKM zeta helps in sustaining long-term memories—and how the inhibition of that enzyme can rapidly erase memories.

Other research demonstrated that the protein CREB can help pinpoint the neurons linked to a particular memory. Findings with a different protein, alpha-CaM kinase II, demonstrated the chemical’s ability to erase both short-term and long-term fear memories in a very targeted fashion. Short-term memory (also called working memory) refers to information stored temporarily. Long-term memory occurs when short-term memories are encoded and stored in a more stable form, so the memory can be retrieved several weeks (and not just several minutes) after a learning experience.

A Molecular Emphasis in Neuroscience

In 1953 a patient known as H.M. unwittingly helped launch the modern era of memory research. To alleviate his severe epilepsy, doctors removed much of H.M.’s medial temporal lobe and part of his hippocampus. The surgery successfully halted the seizures. But it had an unexpected outcome too: It dramatically impaired his ability to form new memories.

H.M.’s memory loss set the stage for significant research gains. In years of subsequent study, H.M. and other patients gave scientists a better understanding of which brain regions orchestrate the conversion of short-term memory to long-term.

Recently, molecular neuroscience has gained prominence in the quest for a more precise understanding of the biological schematic of memory storage. This is no small task. In a 1998 *Neuron* article, researchers Brenda Milner, Larry Squire and Eric Kandel wrote: “In all the fields of all of science, the problems of cognitive neuroscience—the problems of perception, action, memory, attention and consciousness on an intellectually satisfying biological level, offer the most difficult and greatest challenge for the next millennium.”


More than a decade ago, research had already begun to illuminate the vital role of specific proteins in memory storage. One example is cyclic-AMP response-element-binding protein, or CREB. In both fruit flies and sea slugs, early studies identified CREB’s role in converting short-term memories to long-term ones. By the mid-1990s, studies had already suggested a basic difference in the molecular mechanisms of short-term versus long-term memories: The latter required new protein synthesis, while the former did not.

New Research Facilitates Forgetting

Most people would like to boost the amount of information they can retain. But for some, the key to improved quality of life rests with the selective erasure of memory. The purpose is not to blot out trivial event recollections—like an awkward blind date—but to alleviate the debilitating effects of post-traumatic stress disorder, phobias and other memory-related clinical conditions.

To that end, recent research suggests that fear memories can be rapidly erased and that specific proteins have significant powers to abolish them. The results help shed light on the underlying mechanisms that govern these memories.

In October 2008, neurobiologist Joe Tsien and his colleagues published a paper that demonstrated the selective deletion of fear memories in mice. During the embryonic stage, the animals were injected with a DNA molecule that caused their brains (when fully developed) to constantly overexpress a protein called alpha-CaM kinase II. Joe Tsien and colleague conditioned fear in mice, and then successfully deleted the fear memories by overexpressing the protein alpha-CaM kinase II.

(Courtesy of Joe Tsien / Medical College of Georgia)
kinase II. But the protein’s activity was controlled by carefully timed injections of an inhibitor, so the researchers could choose when it would be overexpressed.

They placed the animals in a chamber where the mice heard a tone and then received a mild shock. That conditioned the mice to

Graphs a, c, and e show actual fear response over the three days of the experiment, while graphs b, d, and f show fear expectancy over the same period. Three types of stimuli were presented: fear condition (CS1 = slide + shock), control (CS2 = slide only), and noise alone (NA = background noise present at all times). Day 1 (acquisition): Participants were shown two different frightening slides of spiders. One image (CS1) was always followed by a shock, while the second (CS2) was not. In noise alone, only background noise was presented. Participants were asked to learn how to predict when they would be shocked.
fear both the chamber and the tone. Later, the rodents were placed in a different chamber—but before the tone was played again, the researchers caused the overexpression of alpha-CaM kinase II in the animals’ brains. This time, the mice did not fear the tone; they seemed to have no memory of it as a precursor to painful electric shocks.

Day 2 (extinction): Participants were given either propanolol or placebo, and were then shown the slides again. CS1-R (graphs a – d) represents the reactivation of the fear memory before propanolol or placebo was administered, whereas those shown in graphs e – f did not have the memory reactivated.

Day 3 (test): After sufficient time for propanolol to be washed from the system, participants were again shown the slides. The lack of startle response by those given propanolol before reactivation of the memory (graph c) shows that the drug affected memory reconsolidation. (Copyright Nature Neuroscience 2009 12:256-258)
The researchers found that when alpha-CaM kinase II was overexpressed in the animals during memory recall, it could erase both short-term and long-term fear memories.

One of the most promising results was the targeted nature of this memory deletion. Tsien and his colleagues found that when alpha-CaM kinase II was overexpressed, the memory being retrieved was the only one affected—other fear memories in the mice remained intact.

The selective erasure of a fear memory also opened the door to better understanding of such memories. That was the case with research conducted by the University of Toronto’s Sheena Josselyn and her colleagues. Published in March 2009, the research focused on CREB. This particular protein served as a marker to help researchers address a long-standing challenge: how to identify the neurons that support a particular memory. Instead of gathering in tidy, easy-to-spot bundles, the neurons linked to a specific memory tend to be scattered throughout a brain region.

Josselyn and her colleagues addressed this challenge with an experiment that trained mice to fear a tone. Josselyn’s previous work had suggested that when auditory fear memories form, they tend to recruit amygdala neurons with high levels of CREB. Building on that, the researchers wondered how fear memories would function if those CREB-rich neurons died. In this case, the animals trained to fear the tone were genetically engineered mice, with CREB-rich neurons that could be killed by a diphtheria toxin.

When a random assortment of neurons—not just CREB-rich ones—were eliminated, the mice still feared the tone. But after receiving the toxin that deletes neurons with high CREB levels, the animals stopped fearing the tone. That effect lasted over the twelve days of the experiment, suggesting permanent memory erasure. This didn’t impair the animals’ overall capacity for learning, however. They continued to encode new memories after the toxin destroyed specific CREB-rich neurons.

Some recent work with human subjects has focused on erasure as well—not of a memory but of its emotional component. Merel Kindt and her colleagues at the University of Amsterdam published a paper on this topic in March 2009.

Previous studies pioneered by James McGaugh and colleagues at the University of California-Irvine had demonstrated that memories can be artificially altered when they are recalled, or remembered by administering a substance called propanolol. This alteration is
possible through a process called reconsolidation—when a memory is retrieved, it temporarily loses stability and can be strengthened or weakened. Kindt and her colleagues studied how reconsolidation might be affected by a beta-blocker called propranolol (Inderal). Approved by the FDA as a blood-pressure drug, Inderal has also been used by musicians and other performers to combat stage fright.

The Dutch researchers didn’t force test subjects to perform onstage, but they did create a fear memory by showing them photographs of spiders and then administering a mild electric shock. After subjects had been conditioned to associate spider images with shocks, half of them received a dose of propranolol. Then all of the subjects were exposed again to the spider photos and the shock, reactivating the fear memory. The result: Subjects who received propranolol showed a loss of fear response the next day. The drug dulled the emotional component but did not delete the memory of the experience. The subjects’ “declarative” memory, which encompasses facts and events, remained intact.

The propranolol blocks adrenaline receptors concentrated in the amygdala, where fear memories are believed to be stored. By interfering with the reconsolidation of fear memories, additional treatment options may emerge for patients with post-traumatic stress disorder and other fear-related conditions.

### Memory’s Building Blocks

For decades, researchers have recognized the instability of newly formed memories—that is, short-term memories are particularly vulnerable to change and can be easily weakened. Still, the molecular and cellular underpinnings of that malleable state have remained unknown. One recent example of progress in this area is Joe Tsien’s work with the protein alpha-CaM kinase II in mice. Having shown earlier that over-expression of the protein could delete an established fear memory, Tsien wanted to know if elevated levels of the protein could derail short-term memory. That was the case when researchers boosted alpha-CaM kinase II activity in mice within ten minutes of engaging the animals in a learning activity—it stunted short-term memory formation. Researchers found that the timing is critical. When the same alpha-CaM kinase II alteration took place fifteen minutes after the learning activity, it did not result in a disruption of short-term memory.
In the realm of long-term memory, one molecule that has generated significant interest is PKM zeta. This enzyme became prominent in 2006, when Todd Sacktor and his colleagues at SUNY Downstate Medical Center published a paper suggesting that PKM zeta was needed to maintain long-term memories.6

“It used to be thought that long-term memory was due to structural changes in the brain that were permanent because they were structural,” said Sacktor. “The idea was that once you make a synapse, that’s it—you can forget about the memory maintenance part.”

In contrast, Sacktor’s work shows that PKM zeta is an integral part of long-term memories’ molecular upkeep. In 2009 he reinforced his previous PKM zeta research with a study that inhibited the enzyme and then assessed the effect on long-term memory.7 Sacktor and his colleagues set this up by creating a taste aversion in rats. They exposed them to a new taste—such as saccharin—and then followed it with a lithium dose that sickened the animals. Not surprisingly, the rats avoided drinking from water bottles with saccharin—that is, until they

Using a compound called ZIP to inhibit the memory-maintenance protein PKM zeta, scientists caused rats conditioned with a taste aversion to forget the conditioned stimulus. Rats were trained in a single conditioning session and then given ZIP either 3 or 7 days later, or trained in two sessions one day apart, and given ZIP 25 days later. In all cases, the rats infused with ZIP (black) forgot the conditioning, as indicated by their low level of aversion when compared with rats not injected with ZIP (gray). (Copyright Science 2009)
were injected with a PKM zeta inhibitor, called ZIP. After the rats received a dose of ZIP, their memory of the taste aversion was rapidly erased. The researchers were able to delete three-month-old memories in the rats, but found that inhibiting PKM zeta had no effect on short-term memory. This bolstered previous work, published by Sacktor and his colleagues in 2007, in which the inhibition of PKM zeta wiped out rats’ taste-aversion memories several weeks after they initially formed.8

PKM zeta poses many unanswered questions for researchers. One example is its possible connection with the memory-loss process in Alzheimer’s. One study located the enzyme within the tangles found in the brains of Alzheimer’s patients.9

Sacktor posed a broader question: “Is it possible to enhance people’s memories by giving a drug that will increase the synthesis of PKM zeta?” He said it could be, citing other researchers who found that, in fruit flies at least, an influx of PKM zeta can convert short-term memories into long-term ones.10

**Improving Memory for Better Health—or a Competitive Edge**

Aside from the implications for treating certain disorders, neuropharmacology products that affect memory and cognition are also sought by healthy people looking to improve performance at work or in school.

An online poll, published in April 2008, hints at the desire to find a shortcut to that intellectual edge, particularly in competitive fields. Conducted by *Nature*, the poll invited academics and scientists to disclose whether they had sought a memory boost via drugs approved for treatment of narcolepsy and ADHD. Of the 1,400 respondents, one in five reported taking methylphenidate (Ritalin), modafinil (Provigil) or beta-blockers to improve memory and concentration.11

Anjan Chatterjee, neurology professor at the University of Pennsylvania, anticipated this trend in 2004 when he published an article titled “Cosmetic Neurology” in a science journal, asserting that government regulation of the development of cognitive enhancers seemed unlikely.12 He expanded on that discussion in 2009, arguing in a *British Medical Journal* article that it is unacceptable for people to take methylphenidate (Ritalin) for performance-enhancement reasons.13

Aside from ethical concerns, Chatterjee wrote that the most obvious objection to this use of methylphenidate is that “the cognitive benefits
are minimal and the medical risks are not.” He noted that the U.S. Food and Drug Administration gave methylphenidate the most alarming of possible health warnings because of its high potential for abuse as well as risks of sudden death and serious cardiovascular complications. Medical side effects aren’t the only potential problem, he noted: “There are also possible cognitive trade-offs. For example, greater focus from long term use of methylphenidate could plausibly produce a loss in creativity, which generally requires a loosening of mental boundaries. Such trade-offs are rarely considered or investigated.”

Another treatment that may one day be sought for memory enhancement purposes is deep brain stimulation, which involves implanted electrodes in the brain (see chapter 2, “Deep Brain Stimulation”). Used most commonly for Parkinson’s disease, this treatment is also being studied for conditions such as intractable depression, cluster headaches and phantom limb pain. It may also have the potential to enhance the existing memory circuits of early-stage Alzheimer’s patients—or give a memory boost to otherwise healthy individuals.

A glimpse of that potential appeared in the *Annals of Neurology* in January 2008, in a documented case at a Canadian hospital. An obese man sought DBS as a possible treatment to curb his appetite. With the electrodes stimulating his hypothalamus, the man’s working memory showed significant improvement—and his IQ increased by nine points.14

Changing a patient’s diet could be a less invasive approach to boosting memory, according to a recent study in the *Proceedings of the National Academy of Sciences*. In Germany, a group of healthy adults ages fifty to eighty demonstrated a 20 percent improvement in verbal memory scores after reducing their calorie intake by 30 percent during a three-month period.15

### The Pursuit of Plasticity

During the past decade, assumptions about the brain’s ability to rewire neurons’ connections in response to experience have changed dramatically. Synaptic plasticity was once primarily associated with youth. But research in the late twentieth century—including a 1999 study of neuron growth in the hippocampus of adult monkeys—marked the start of a shift in that scientific outlook.16 Now studies have shown that plasticity can extend well beyond childhood, if only in a relatively diminished capacity.
To recruit plasticity to help prevent age-related cognitive decline, researchers must first piece together the structural and functional changes behind this basic framework of memory formation. A molecule called myosin Vb may be indispensable to that framework, according to a study published in October 2008. Researchers observed that the myosin molecule in a rodent’s hypothalamus facilitated the movement of new receptors, which in turn strengthened synaptic connections. When researchers blocked myosin, it prevented the addition of new receptors. This molecule could represent a new target for the treatment of diseases involving synaptic abnormalities, such as Alzheimer’s or autism.¹⁷

By studying postnatal mice, researchers have also identified a protein that triggers plasticity in visual systems. Published in August 2008, the research highlighted the role of orthodenticle homeobox 2, or Otx2. This protein facilitates the maturation of parvalbumin cells, located in the visual cortex, which help rewire the brain in response to visual input. Evolutionary biology shows that Otx2 developed from a protein in fruit flies called orthodenticle, which helps determine head development and was first described by researchers R. Finkelstein and N. Perrimon.¹⁸ Otx2 is a protein that facilitates the maturation of parvalbumin-expressing cells. Located in the visual cortex, these neurons help rewire the brain in response to visual input.

One surprising result from this study: Otx2 is synthesized by the retina, then migrates to the cortex. Essentially, the eye is dictating plasticity timing for the brain. The study’s senior investigator, Takao Hensch of Children’s Boston Hospital, speculates that the visual system may not be the only sensory system that includes a molecular plasticity trigger like Otx2. If researchers can one day control the timing of plasticity, they could address a range of needs, such as learning a language or recovering from a stroke.¹⁹

Conclusion

The story of memory research has been long and now turns out to be wide as well, involving such disorders as post-traumatic stress disorder, which concerns the persistence of unwanted memories, and Alzheimer’s, in which memory deficiency is a symptom of the problem.

For those patients, memory research has dramatic potential to improve quality of life. To that end, scientists continue to work
toward bridging the gap between laboratory results and treatments intended for clinical applications. But that’s not the only challenge. Scientists—and society at large—must resolve ethical questions that accompany the manipulation of memory. If we do find a drug that can give memory a turbo boost, how should it be regulated—and will it carve out an intellectual divide that creates unfair advantages?

To optimize the way memory functions, scientists must continue to map out its inner workings at the molecular level. Recent research underscores the role of specific proteins for preserving memory. In addition, scientists have shown that rapid erasure of memory may someday become a reality.

As the next chapter of memory research unfolds, scientists like Joe Tsien expect it will be action-packed. “For the next five years, you will really see an explosion of our understanding in terms of the general organizing principles of memory,” said Tsien. “Once you understand that, then you can have a whole new way of looking at all sorts of memory disorders. The electrical patterns in the population network of these neurons—that’s where I think the interesting things are; that’s where the important work lies ahead.”
The accumulation of beta-amyloid (shown here as brown spots) is increased in mice that are depleted of testosterone (left) and reduced in mice given extra testosterone (right).

(Courtesy of Christian Pike / University of Southern California)
While much has been learned about neuroprotection—the mechanisms and strategies by which the brain responds to neuronal injury or the early stages of a disease—still more about these abilities remains unknown. Researchers are now pursuing several lines of investigation to understand the nature of neurons’ ability to protect themselves and to recruit this capacity in disease prevention and therapy. The protective influences they are studying range from common molecules in the brain to lifestyle choices such as diet and exercise.

Ever since Italian neuroscientist Rita Levi-Montalcini’s 1952 discovery of nerve growth factor, a molecule that promotes the survival and differentiation of neurons, scientists and drug companies have sought to find and use molecules and chemicals that work similarly to protect the central nervous system. Twenty years ago, investigations on neuronal damage in stroke and spinal cord injury led to studies of growth factors and other ways to protect and repair nerve cells from both kinds of injuries. To date, however, the FDA has approved only two neuroprotective agents: riluzole for amyotrophic lateral sclerosis (ALS) and memantine for moderate to severe Alzheimer’s disease.

Research in 2009 helped to explain some of the mechanisms of neuroprotection, as well as ways to foster greater protection of brain cells and thereby help control the aging process. In particular, scientists this year studied the protective qualities of a family of enzymes called sirtuins, sex hormones such as estrogen, and vitamin D.

Proteins Constantly Protect the Brain

Researchers have found that the brain produces certain chemicals to help protect neurons, including several that encourage neuronal growth and allow some parts of the brain to take over the function, to some extent, of areas damaged by illness or injury. Scientists first identified heat shock proteins, a class of proteins that become especially active when cells are exposed to elevated temperatures and stress, in the 1970s. They have been reported to increase cell survival in response to a wide range of cellular stressors. One of these proteins, heat shock protein-70 (HSP-70), is reported to protect against oxidative stress, an oxygen imbalance that leads to the formation of highly reactive molecules called free radicals.1
Oxidative damage from free radicals has been implicated in a number of diseases, including Alzheimer’s.

Scientists discovered brain-derived neurotrophic factor, or BDNF, in the 1980s. BDNF is a member of the neutrophin family of proteins and acts on certain neurons in the brain and spinal cord, helping to maintain the health of existing neurons and encouraging the growth and differentiation of new neurons and synapses after injury. BDNF is particularly active in the hippocampus, cortex and basal forebrain, areas vital to learning and memory, where neurons regularly make new connections, and, in the case of the hippocampus, new neurons are born throughout life. Studies have linked reduced levels of BDNF to neurodegenerative diseases such as Alzheimer’s and Parkinson’s, suggesting that, in adequate amounts, this natural protein may prevent the cell death caused by those underlying diseases.²

Now scientists are adding more chemicals to their neuroprotection list, including a family of enzymes called sirtuins, which are considered universal regulators of aging in virtually all living organisms, from fruit flies and worms to humans.

Sirtuins have numerous health benefits, including providing protection against neurodegenerative diseases such as Alzheimer’s and ALS, and increasing the number and function of mitochondria (a cell’s energy factory), the dysfunction of which is associated with progressive neuronal degeneration. Caloric restriction activates sirtuin proteins. Resveratrol, an antibiotic produced naturally by some plants when under attack by pathogens such as bacteria or fungi, is a potent activator of SIRT1, one of the seven sirtuin proteins, which also aids in cell survival and neuroprotection.

In 2006 David Sinclair of Harvard Medical School published two papers showing that resveratrol, which is found in the skin of red grapes and is a major constituent of red wine, could reduce the impact of a high-fat diet, increase stamina and extend the life span of mice. A follow-up study published in Nature by Sinclair’s colleagues at Sirtris Pharmaceuticals demonstrated that novel drug compounds, based on SIRT1, offer a promising new approach to treating age-related diseases.³

“The new drug candidates represent a significant milestone because they are the first molecules that have been designed to act on genes that control the aging process. For this reason, we feel they have considerable potential to treat diseases of aging,” said Christoph Westphal, who led the research team.
Drinking red wine is considered unlikely to provide the desired neuroprotective effects. In a 2009 paper in *Expert Opinion in Therapeutic Patents*, however, Francisco Alcain and José Villalba of the University of Cordoba, Spain, pointed out that new SIRT1 activators are up to one thousand times more effective than the resveratrol found in grapes and wine. High doses of natural resveratrol might not be sufficient to produce a neuroprotective effect, they said, arguing that scientists need to develop new synthetic sirtuin activators.

Researchers at the MassGeneral Institute for Neurodegenerative Diseases (MIND) reported in the July 2007 issue of *Science* that blocking the activity of another sirtuin protein, SIRT2, may be an effective therapy in Parkinson’s disease. The scientists, led by Aleksey Kazantsev, director of MIND’s drug discovery laboratory, found that blocking SIRT2 activity could protect neurons damaged by the toxic effects of alpha-synuclein, a protein that accumulates in the brains of Parkinson’s patients (see chapter 3, “Parkinson’s Disease”).

Some scientists believe that alpha-synuclein folds abnormally in dopamine-producing neurons in Parkinson’s patients, forming toxic-inclusion bodies, clumps of the protein that lodge inside and kill or impair these cells. In 2006, the MIND investigators studied a laboratory chemical called B2 that reduces toxicity in cellular disease models, and found that inhibition of SIRT2 reduced the toxicity of alpha-synuclein. On the basis of the B2 structure, Kazantsev and
his team developed a SIRT2 inhibitor, called AGK2, that is ten times as potent as B2. The findings, said Kazantsev, will allow scientists to pursue innovative new drugs to treat and perhaps even cure Parkinson’s and other neurodegenerative diseases.

**Vitamin D Protects Cognition**

A particularly lively area of neuroprotection research in recent years has been the exploration of evidence that vitamin D (25-hydroxyvitamin D) may have significant neuroprotective features. Vitamin D is found in very few foods. Most people get their intake through sunlight or food supplements, and thus many of the studies have focused on the consequences, particularly in aging, for people with too little of the “sunshine vitamin.”

Low levels of vitamin D are linked to a range of health issues, including weak bones and muscles, certain cancers, high blood pressure and congestive heart failure. Less well known are findings relating insufficient vitamin D to mental illnesses, such as depression and seasonal affective disorder. Studies have also discovered that vitamin D plays a role in neurodegenerative diseases such as Alzheimer’s and Parkinson’s by promoting the production of neurotrophic factors, as well as in cognitive impairment and memory loss.

In 2001 scientists from Taiwan and the National Institute on Drug Abuse reported that vitamin D3, one of the two major active forms of vitamin D, can restore muscle activity in rats induced with Parkinson’s disease. Their study, published in *Brain Research*, showed that treating the rats with D3 improved muscle movement and reduced the dopamine neuronal toxicity caused by the compound given to induce Parkinson’s. The researchers think that the reversal of a toxic mechanism that injures cells via free radicals and reactive oxygen may take place when the D3 is administered.

Studies in 2009 sought to clarify such indications of vitamin D’s neuroprotective role. In a study published in the May issue of the *Journal of Alzheimer’s Disease*, William B. Grant of the Sunlight, Nutrition and Health Research Center in San Francisco presented an analysis of several large studies showing that vitamin D can help reduce dementia.

The development of dementia, a long-term decline in cognitive function progressively worsening beyond what is normal in aging,
involves several mechanisms, including oxidative stress, inflammation and reduced neurogenesis in the adult brain. Epidemiological evidence suggests that vitamin D reduces the risk of several diseases that are risks for or can precede dementia. “It appears that vitamin D metabolites, especially the active form of vitamin D3, can counter many of the mechanisms linked to risk of dementia,” said Grant.

Another study found that vitamin D may offer some protection against the neurodegeneration seen in Alzheimer’s disease, the most common form of dementia. The researchers reported in the Journal of Geriatric Psychology and Neurology that as vitamin D levels decreased in study participants, all over age sixty-five, levels of cognitive impairment rose. Individuals with the lowest levels of vitamin D were more than twice as likely to be cognitively impaired. The association between vitamin D and cognitive impairment was stronger in men. “The cause of dementia is not [simply the lack of] vitamin D,” said David Llewellyn of Cambridge University, the lead author of the study. “It’s a very complicated disease. But while further research is needed, vitamin D supplementation is cheap, safe, and convenient and may therefore play an important role in prevention.”

Adding to this research are findings correlating vitamin D and cognition in middle-aged and older men. Scientists at the University

In older persons, cognitive impairment decreases as the level of vitamin D in the blood increases. (Courtesy of David Llewellyn)
of Manchester compared the cognitive performance of more than 3,100 men, ages forty to seventy-nine, at eight European Male Aging Study test centers in Europe. The men with higher levels of vitamin D consistently performed better on simple tests that measure attention and speed of information processing.

“The positive effects vitamin D appears to have on the brain need to be explored further, but certainly raise questions about its potential benefits for minimizing age-related declines in cognitive performance,” said lead author David Lee.

**Sex Hormones and Neuroprotection**

Sex hormones—androgens (male) and estrogens (female)—affect the growth and function of the reproductive organs, development of sex characteristics, and behavioral patterns. Studies of estrogen during the past twenty years have brought to light a remarkable number of ways in which these hormones do far more than serve reproduction. Scientists have come to recognize that estrogen is an important neurotrophic and neuroprotective factor and have implicated it in cognition, synaptic plasticity, memory and neurogenesis.

As we age, levels of sex hormones in the blood and brain begin to decline. Many of estrogen’s neuroprotective actions are relevant to Alzheimer’s disease prevention, including reducing beta-amyloid accumulation, a critical factor in Alzheimer’s progression, and reduced plasticity in neuronal dendritic spines, which serve as storage sites for synaptic strength. Studies suggest that reduced estrogen levels in women and age-related testosterone loss in men can contribute to the development of Alzheimer’s disease.

In the late 1990s German scientist Christian Behl discovered that estrogen can also act as an antioxidant. His research demonstrated that in high levels estrogen reduces the neuron-killing effects of free radicals by making free radicals less toxic to neurons. Later, Bruce McEwen of Rockefeller University showed that estrogen has the potential to improve mental function by enhancing neuronal survival in the hippocampus, where, his team discovered in rats, estrogen helps to build and maintain new synapses.

In 2008 Colin Saldanha of Lehigh University discovered that in the brains of birds and mammals that have sustained brain injuries, testosterone is converted into estrogen, a process that can decrease
neuronal degeneration and may enhance the recovery of neurons. In
the July 2009 issue of *Frontiers in Neuroendocrinology*, Saldanha and
his colleagues reported that the expression of aromatase, an enzyme
responsible for a key step in the synthesis of estrogen from testoster-
one, can raise estrogen levels enough to interfere with apoptosis,
or programmed cell death, and ultimately lessen the extent of damage
from brain injuries. This activity appears to protect neurons by
slowing down the degeneration of the damaged cells and increasing
the speed with which they are repaired.

Recent data suggest that the elevation of estrogen levels by
aromatase selectively activates certain signaling pathways such as the
blocker of programmed cell death, Akt. “While a direct link between
aromatase and Akt signaling remains to be established, this interac-
tion presents a promising explanation of the neuroprotective effects
of brain aromatase,” Saldahna and his colleagues wrote.

One of the most common neurodegenerative diseases, Parkinson’s
occurs in greater numbers and may progress more quickly in men than
women, suggesting that estrogens may confer some resistance to the
development and progression of the disease, according to researchers
at Laval University Medical Center in Quebec. In the lab, the
scientists studied the use of various sex hormones, including estra-
diol, progesterone and androgens, in a mouse model of Parkinson’s.
They found that only estradiol had a neuroprotective effect on the
animals’ dopamine.

In a review of the research, published in *Frontiers in
Neuroendocrinology* in July 2009, a team of scientists led by Christian
Pike of the University of Southern California evaluated evidence that
estrogens and androgens may help in the prevention of Alzheimer’s
disease. They found that experimental studies indicate that estro-
gens reduce neuron loss in Alzheimer’s and also reduce levels of
beta-amyloid, while androgens promote “survival in neurons chal-
enged with AD-related insults and reduction of beta-amyloid levels.”
In addition, they found that estrogen prevents beta-amyloid accumu-
lation by regulating programmed cell death.

Pike’s team concluded that androgens protect the brain against
Alzheimer’s by promoting the survival of neurons in the hippocampus
and cortical regions. They also found that androgens limit the accu-
mulation of beta-amyloid and protect the brain against the formation
of tau protein, abnormal amounts of which are found in the brains of
Alzheimer’s patients.
The authors noted that current treatment research focuses on the development of compounds called SERMS (selective estrogen receptor modulators) and SARMS (selective androgen receptor modulators) to treat Alzheimer’s. In low concentrations, SERMS have been shown to protect cultured neurons from beta-amyloid toxicity. Androgen-based therapy with SARMS is also drawing considerable interest in the scientific community.

**Natural Neuroprotection**

In addition to these mechanisms of neuroprotection, simple lifestyle choices—such as eating healthy foods, maintaining a healthy weight and engaging in physical and mental exercise—have also been shown to reduce susceptibility to some brain diseases.

The risk for Parkinson’s disease is moderately lower in people who are physically active, according to a Harvard University study from January 2008, which followed more than 143,000 participants for ten years. Similarly, researchers from the Group Health Cooperative in Seattle reported a 40 percent lower incidence of Alzheimer’s among study participants who performed light or moderate exercises, such as walking, dancing, jogging, or swimming, more than three times per week compared with those who did these exercises less frequently. The researchers, who followed 1,740 participants and measured their exercise frequency, cognitive function and potential risk factors for dementia, said exercise helps foster healthier blood vessels and better blood flow, which may ward off disease.
In addition, moderation in drinking, abstaining from smoking and maintaining a healthy weight may all help protect neurons as well, albeit through mechanisms that are not yet clear to researchers. At a presentation at the 2008 conference of the American Academy of Neurology, scientists from Mount Sinai Medical Center in Miami reported that Alzheimer’s patients who drank more than two beers per day when young went on to develop the disease nearly five years earlier than those with lighter drinking habits. They also found that patients who smoked more than a pack of cigarettes a day developed Alzheimer’s almost two years earlier than those who smoked less or not all. Another study determined that people with high cholesterol, obesity, or beer bellies in their forties were more likely to develop Alzheimer’s later in life.

Scientists also know that an intellectually and socially active brain is more resistant to disease. In an animal study, University of Chicago researchers discovered that when neurons are active and firing, nearby microglial cells release low levels of tumor necrosis factor-alpha (TNF-alpha). When released in large amounts, TNF-alpha can kill neurons. The Chicago scientists found, however, that at concentrations well below these lethal levels, TNF-alpha can actually protect neurons from toxic or injury-related damage. TNF-alpha, they said, causes neurons to increase their production of as yet unidentified growth factors that repair DNA and defend against injury.

**Conclusion**

Although hundreds of molecules—from free radical scavengers and apoptosis inhibitors to neurotrophic factors—have been investigated for their neuroprotective properties, there has been little success in moving these potential treatments from the laboratory to human trials, for a number of reasons. Animal models do not often accurately simulate diseases in humans. The pathophysiology of diseases in humans differs from that in animals. And most laboratory animals have smaller brains than humans.

Despite these challenges, scientists continue to focus their work on advancing neuroprotection as a desired therapy for neurodegenerative diseases and brain injuries. Building on studies from the past two decades, findings from the 2009 research on sirtuins, sex hormones and vitamin D have taken them a step closer to that reality.
Researchers at the Children’s Hospital of Philadelphia compare DNA to identify copy number variations associated with autism spectrum disorder.

(Courtesy of Hakon Hakonarson / Children’s Hospital of Philadelphia)
Fruit Flies Lead to Insights Into Function of Sleep

Two studies of fruit flies published in 2009 provide experimental support for a recent hypothesis on why we sleep.¹ The “synaptic homeostasis” hypothesis suggests that sleep plays an important role in “downscaling” or reducing synapses, the connections between brain cells, which if allowed to increase without control, would take up too much space in the brain. The hypothesis is based on the assumption that synaptic strength is generally increased during waking periods, and that this increase in strength requires both energy and physical space in the brain and would be unsustainable without an opposing process of reduction.

A group of researchers from the University of Wisconsin, including Giulio Tononi and Chiara Cirelli, who initially proposed the synaptic homeostasis theory, looked at levels of synaptic proteins in fruit flies after a period of wakefulness and after a period of sleep.² They discovered that levels of these proteins, thought to be markers of synaptic activity, were high after waking and progressively declined during sleep. This study adds to earlier work showing similar results in rats.

The other study, conducted by Paul Shaw and colleagues from Washington University in St. Louis, Missouri, looked at the effects of daytime activities on sleep.³ The study was a follow-up to previous studies that showed that the level of synaptic proteins, thought to indicate synaptic activity, is low after a period of sleep (left) and high after being awake (right) in most regions of the fruit fly brain.

(Courtesy of Chiara Cirelli / University of Wisconsin)
research showing that fruit flies sleep longer after exposure to socially enriched environments (consisting of groups of thirty or more male and female flies). Shaw and his fellow researchers identified three genes necessary for this increased sleep response. Flies without any of these genes did not show an increase in sleep after stimulation. Replacement of the genes in ventral lateral neurons, which are in the part of the fly brain that controls behavior in response to the circadian clock, was enough to restore the sleep response. This result suggests that these neurons may be involved with regulating the need for sleep.

The researchers also discovered an increase in the number of synapses in the flies after social stimulation, along with a decrease after sleep, supporting the hypothesis that sleep is involved in down-scaling synapses. “For me it was a surprising outcome,” said Shaw, who admitted that he was previously skeptical of the synaptic homeostasis hypothesis. “I still think it’s probably more complicated than just [Tononi’s] model, but it’s the data that matters the most.”

However, other research conducted by a team from the University of Pennsylvania, published in the February 2009 issue of *Neuron*, appears to contradict the theory. Looking at the consolidation of learning and memory in cats, researchers discovered that sleep strengthened synaptic connections in the visual cortex after a waking period when the cat was deprived of sight in one eye.

The authors of the study suggested that differences between their findings and previous results supporting synaptic homeostasis may be related to the different types of plasticity being studied in each case, as well as the nature of the changes taking place when the measurements were made.

**New Targets for Treating Age-related Macular Degeneration**

Age-related macular degeneration (AMD) is one of the leading causes of blindness worldwide. Now increased understanding of the disease is helping scientists to develop new ways to diagnose and treat it.

There are two forms of macular degeneration, so called because the disease affects the macula, the central part of the retina where the visual receptors are most dense and provide the highest visual acuity. In the “dry” form of AMD, the macula thins and dries out, causing the loss of central vision. The more severe neovascular or “wet” form
is accompanied by the growth of new blood vessels in the choroid, a layer of vessels below the retina, a process known as choroidal neovascularization (CNV), a form of angiogenesis. The new blood vessels leak blood and fluid into the retina, disturbing vision and in many cases resulting in blindness.

Over the past few years, treatment approaches for neovascular AMD have focused on anti-angiogenesis therapy, in particular agents that block a molecule called vascular endothelial growth factor (VEGF), which stimulates angiogenesis in the cells lining the blood vessels. A 2008 Cochrane Review of anti-VEGF agents in the treatment of neovascular AMD found that the two anti-VEGF agents included in the review, pegaptanib and ranibizumab, both reduced the risk of visual acuity loss in patients with neovascular AMD. The report concluded that “anti-angiogenesis therapy modalities provide a promising means of treating the potentially devastating problem of AMD.”

In a 2009 paper published in Retina, Martin Friedlander from the Scripps Research Institute reported on a study of neovascularization in mice showing that a combination of anti-angiogenesis therapies, targeting different pathways of new vessel formation, was more effective in inhibiting neovascularization than a single angiogenic inhibitor, even a VEGF inhibitor. He wrote: “If the goal or one of the goals in AMD treatment is to fully inhibit choroidal neovascularization, then combination therapies will be essential.”

Another potential therapeutic target for AMD was identified by a team of researchers led by Jayakrishna Ambati, from the University of Kentucky, Lexington. They discovered a protein receptor, CCR3, on the surface of blood vessels in CNV tissue taken from patients who had the neovascular form of the disease. CCR3 is not found in normal vascular tissue, suggesting that it is a biological marker for CNV. Ambati and colleagues then looked at the effects of CCR3-blockade (induced either genetically or pharmacologically) in mice with CNV and found that it suppressed neovascularization. They also found CCR3 inhibition to be slightly more effective at reducing CNV than VEGF inhibition.

More interesting to Ambati and colleagues was the potential for using CCR3 as a marker for CNV before vision loss occurs. Using a method to track CCR3 antibodies in the mouse model, they were able to detect the new blood vessels before they penetrated the retina, something that was not previously possible. The results of the study were reported in Nature in June 2009.
Hope for early diagnosis or risk assessment also comes from recent genetic studies of AMD. In a 2009 review paper published in *Current Opinion in Ophthalmology*, Ian MacDonald and colleagues from the University of Alberta wrote: “First-degree relatives of patients with AMD tend to have a higher risk of AMD. Recognizing an inherent genetic risk of AMD in these patients will improve their management and potentially help prevent blindness.”

A Step Back for New Drug Class for Treating Schizophrenia

A key trial for a new class of schizophrenia drugs yielded inconclusive results in 2009, a disappointing outcome for researchers studying this challenging disease.

Schizophrenia is a complex mental disorder, with symptoms that include hallucinations, delusions, social withdrawal and problems with attention and memory. Many of the currently prescribed antipsychotics have significant side effects and are not very effective in improving cognitive and psychological function.

An industry announcement at the International Congress on Schizophrenia in March 2009 reported that a promising candidate for a new class of drugs showed inconclusive results in a Phase II clinical trial, dampening hopes that a new treatment option for schizophrenia was within close reach.

Antipsychotics have traditionally adjusted the regulation of the neurotransmitter dopamine in the brain, although there is no solid evidence that schizophrenia is the result of a primary dopamine abnormality. In 2007 a drug affecting activity of the neurotransmitter glutamate, thought to be an important element in the pathology of schizophrenia, showed promise in a “proof-of-concept” clinical trial. The new compound, known as LY2140023, activates specific glutamate receptors, the metabotropic glutamate receptors, or mGlur; it is thought to work in part by reducing the release of glutamate at the synapses of brain circuits regulating emotional and motivational behavior. The results of the 2007 study by Darryl Schoepp and colleagues at Eli Lilly were published in *Nature Medicine*.

The results of the initial trial showed improvement in outcomes for LY2140023 compared with placebo, and comparable safety and tolerance with an existing antipsychotic, olanzapine. Daniel Weinberger
from the National Institute of Mental Health noted in an accompanying commentary that this was the “first credible evidence” of an effective antipsychotic drug that did not target dopamine.  

In the follow-up Phase II trial, involving a larger number of patients, in 2009, however, LY2140023 did no better than a placebo. A higher than normal placebo response was seen both against LY2140023 and against olanzapine, which was used as a control drug in the trial. Despite the inconclusive results, Eli Lilly has said it will go ahead with drug development. An additional Phase II study is being planned to test the molecule in hopes of validating the proof-of-concept trial results. Lilly expects the trial to begin sometime in the first half of 2010.

**Piecing Together a Complex Puzzle**

Autism spectrum disorders (ASDs) are characterized by a broad set of symptoms that include varying degrees of social, cognitive and communication dysfunctions that usually emerge within the first few years of life. New studies of large groups of children with ASDs and their families are allowing researchers further insights into the biological nature and heritability of these disorders.
A research team led by Hakon Hakonarson of the Children’s Hospital of Philadelphia conducted a genome-wide analysis of 912 families with more than one affected child and compared the results to DNA from families without such disorders. They identified twenty-seven different genetic regions with rare copy number variations (CNVs), genetic variations associated with missing or extra copies of DNA segments. Some CNVs had been previously associated with ASDs. The new study also identified several genes potentially involved in the pathophysiology of ASDs, including a previously reported gene involved in brain development and known as neuronal-adhesion gene NRNX1, and two new genes, BZRAP1 and MDGA2, that also are believed to be important in neuronal development.

An earlier 2009 study by Hakonarson and colleagues, looking at the DNA of 780 families with children affected by an ASD, identified common genetic variations in ASD cases on a region on chromosome 5 (named 5p14.1), between the neuronal-adhesion genes, cadherin 10 and cadherin 9. The same results were also achieved in a smaller independent study led by Margaret Pericak-Vance from the Miami Institute for Human Genomics.

While this gave some evidence that common variants are involved in ASDs, Pericak-Vance and colleagues wrote that it is “highly unlikely” that a strong single-gene association, such as the association of the APOE gene in Alzheimer’s, will be identified in autism. Rather, they concluded, “our results, in combination with the multiple rare
variants already identified, suggest that the genetic architecture of autism is as exquisitely complex as its clinical phenotype.”

Both of these studies added to a growing body of evidence implicating neuronal-adhesion genes in ASDs. Neuronal cell-adhesion molecules play a vital role in various cell processes, including enabling neurons to connect with each other. Given these genetic findings, along with anatomical and functional imaging studies, Hakonarson and his fellow researchers postulate that ASDs may represent a neuronal disconnection syndrome.

Researchers and clinicians are also working to clarify and standardize the clinical criteria for ASDs and to better understand the onset of these disorders. Typically, onset of autism is categorized as “early,” when symptoms such as delayed speech development appear in the first year or so of life, or “regressive,” when initial normal development is followed by the loss of skills in the second year of life. A 2008 review of the literature on autism onset suggested that this classification is too narrow to accommodate the variety of ways in which autism can emerge.15 The review also highlighted the challenges to categorizing onset, including the unreliability of parents’ memories and reporting skills in retrospective studies.

A new endeavor by a group of autism researchers, called the Early Autism Risk Longitudinal Investigation (EARLI), is planning to focus on more than one thousand pregnant women who already have a child with autism and follow them through their pregnancies and deliveries and the first three years of the new child’s life.16 The study, which is being coordinated by the Drexel University School of Public Health in Philadelphia, will look at early risk factors for autism and will include genetic analyses as well as behavioral and developmental assessments in an attempt to put some of the pieces of this complex puzzle in place.
A NEUROSCIENTIST’S PERSPECTIVE ON THE ADVANCES IN THE GENETICS OFPSYCHIATRIC DISORDERS


1. GENETICS: THE EMERGING SCIENCE OF GENE EXPRESSION AND MENTAL ILLNESS


Mulder EJ, Morris AP, Bailey AJ, and Monaco AP. High-density SNP association study and copy number variation analysis of the AUTS1 and AUTS5 loci implicate the IMMP2L-DOCK4 gene region in autism susceptibility. *Molecular Psychiatry* 2009 (Epub in advance of print April 28, 2009).


2. DEEP BRAIN STIMULATION: BEYOND MOVEMENT DISORDERS


### 3. PARKINSON’S DISEASE: A PARADIGM SHIFT


### 4. MULTIPLE SCLEROSIS: GENETIC STUDIES BEGIN TO UNRAVEL THE MYSTERY

1. Interview with Stephen L. Hauser, MD, Professor and Chair, Department of Neurology, University of California, San Francisco.


5. MEMORY AND FORGETTING: PIECING TOGETHER THE MOLECULAR PUZZLE OF MEMORY STORAGE


7. Shema R, Hazvi S, Sacktor TC, and Dudai Y. Boundary conditions for the maintenance of memory by PKMzeta in neocortex. Learning and Memory 2009 16(2):122–128.


6. NEUROPROTECTION: GUARDING AGAINST INJURY AND DEGENERATION


7. ROUNDUP: OTHER IMPORTANT FINDINGS IN 2009


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INDEX

A

ablatve surgery, 34, 35 
activin A, 55 
AD.  See Alzheimer’s disease 
Addington, Anjene, 27 
adenine nucleotide, 20, 52 
adrenal glands, 13 
age-related cognitive decline, 81 
age-related macular degeneration (AMD), 95–97 
ageing and sirtuin enzymes, 85–87 
Akbarian, Scharahm, 18, 29–30 
Akt and aromatase, 90 
Alcain, Francisco, 86 
alcohol and Alzheimer’s disease, 92 
alpha-CaM kinase II protein, 72, 73–76 
alpha-synuclein protein, 47, 49, 52, 86 
ALS (amyotrophic lateral sclerosis), 8, 84 
Alzheimer’s disease (AD) and BDNF, 85 
and candidate gene strategy, 11 
and DBS, 43 
and estrogens or androgens, 89, 90–91 
and lifestyle choices, 92 
and neuroprotective agents, 84 
research breakthroughs, 19 
and SERM or SARM compounds, 91 
and synaptic abnormalities, 81 
and vitamin D, 87, 88 
Ambati, Jayakrishna, 96 
AMD (age-related macular degeneration), 95–97 
American Academy of Neurology, Miami, 92 
American Journal of Human Genetics, 25–26 
American Journal of Medical Genetics, 32 
amygdala and fear memories, 76 
amyloid precursor genes, 19 
amyotrophic lateral sclerosis (ALS), 8, 84 
androgens and estrogens, 89–91 
angeogenesis in blood vessel linings, 96 
animal models for research, 50–51, 92 
anterior nucleus of the thalamus, 42 
anti-angiogenesis therapy for AMD, 96 
antidepressant medications, 49–50, 97 
antioxidants 
estrogen as, 89 
and Parkinson’s disease, 47, 52–54, 55 
Anxiety, DBS for, 39 
apoptosis, 90 
Archives of Neurology, 49, 54 
area 25 of the subgenual cingulate cortex and depression, 41 
aromatase enzyme, 90 
ARRON (autoimmune-related retinopathy and optic neuropathy syndrome), 69 
Ascherio, Alberto, 52, 53 
ASDs (autism spectrum disorders), 12, 25, 98–100 
astrocytes, 55 
autism early versus regressive, 100 genetic complexity of, 31, 99–100 GWAS studies, 11–12 heritability of, 3, 5, 10, 11–12 neuroimaging research, 1–2 risk genes, 25–27 and schizophrenia, 28 and synaptic abnormalities, 81 autism spectrum disorders (ASDs), 12, 25, 98–100 autoimmune-related retinopathy and optic neuropathy syndrome (ARRON), 69 autosomal dominant genes, 8 
autosomal recessive genes, 8
Avonex (interferon beta-1a), 65
axon degeneration in the dopaminergic system, 50
axons
and damaged myelin, 60–62, 63, 64
and dendrites, 26
and dopaminergic system, 50
and SNPs, 24

B
B2 laboratory chemical, 86–87
basal forebrain, 85
basal ganglia, 37–38
BDNF (brain-derived neurotrophic factor), 85
Beal, M. Flint, 50–51
Behl, Christian, 89
Benabid, Alim-Louis, 35
Berger, Joseph, 67, 69
beta-amyloid peptide, 11, 83, 89–91
beta-HCH and Parkinson’s disease, 49–50
Betaseron (interferon beta-1b), 65
Biological Psychiatry, 30
blood-brain barrier, 60–61, 66
Bostwick, J. Michael, 56
brain cell degeneration from oxidative damage, 52. See also oxidative stress
brain-derived neurotrophic factor (BDNF), 85
brain development, 11, 25, 26, 27. See also childhood abuse and neglect
brain function, 6, 37–38
brain injuries, 6
brain plasticity, 24, 39, 80–81, 92
Brain Research, 87
Brainsway company (Israel), 36
British Medical Journal, 79–80
Burt, Richard, 68–69

C
Calabresi, Peter, 66–67
caloric restriction, 80, 85
candidate gene research strategy, 11
CCRF protein receptor and CNV, 96
cell adhesion molecules, 27
central nervous system (CNS), 60–61
central thalamus, 43
Chatterjee, Anjan, 79–80
childhood abuse and neglect, effect of, 13–14, 30–31
childhood-onset schizophrenia, 27
cholesterol and Alzheimer’s disease, 92
choroidal neovascularization (CNV), 96
choroid and AMD, 95–96
chromosomal 8p region, 14
chromosome 2 SNPs, 22–23, 25–26
chromosome 5 and ASD, 99
chromosome 6 and MHC, 21, 22
chromosome 6 SNPs, 20–21
chromosome 7 IMMP2L and DOCK4 genes, 26
chromosome 8 SNPs, 23
chromosome 11 and MHC, 25
chromosome 15 CNV, 27
chromosome 15g11-13 CNVs, 12
chromosome 16 CNV, 27–28
chromosome 18 and MHC, 25
chromosome 22q11 CNVs, 12, 15
chromosome 22 SNPs, 27
chromosome ZNF533 gene, 26
chronic pain syndromes and DBS, 35
circuit disorder, 37–38
Cirelli, Chiara, 94
cladribine (Leustatin), 66
cluster headaches and DBS, 43
CNS (central nervous system), 60–61
CNV (choroidal neovascularization), 96
CNVs. See copy number variations
cocaine use and Parkinson’s disease, 49–50
Cochrane Review, 96
cognition
and DBS, 42–43, 80
and vitamin D, 87–89
coma and DBS, 43
“common disease, common variant” hypothesis, 3
compulsive gambling, 56
concordance rate for psychiatric disorders in twins, 9, 10
consciousness and DBS, 42–43
Copaxone (glatiramer acetate), 65–68
copy number variations (CNVs)
and autism, 25, 99–100
overview, 12, 24
research on, 15–16
and schizophrenia, 27–28
twin studies, 24–25
cortex, 37–38, 85, 90
corticosterone hormone, 13
“Cosmetic Neurology” (Chatterjee), 79–80
Coyle, Joseph T., 8–16
CREB (cyclic-AMP response-element-binding protein), 6, 71, 73, 76
Crohn’s disease, 69
culprit genes. See risk genes
Current Opinion in Ophthalmology, 97
cyclic-AMP response-element-binding protein (CREB), 6, 71, 73, 76
Cytosine nucleic acid, 14
cytosine nucleotide, 20

D

Darwin, Charles, 13
DBS. See deep brain stimulation
deep brain stimulation (DBS)
and brain plasticity, 39
and cluster headaches, 43
and consciousness, 43
and epilepsy, 42
future of, 43–44
and genes, 38–39
and memory, 42–43, 80
multiple uses for, 35–37
and obesity, 42–43, 80
overview, 5–6, 33
and Parkinson’s disease, 6, 35–38, 56–57
and psychosurgery stigma, 34–35
and rhythm of brain signals, 37–38
and Tourette’s syndrome, 42
depth TMS, 36
DeLong, Mahlon, 35, 46–47, 48, 49–50, 54, 57
dementia, 87–89
dementia with Lewy bodies, 48, 49
“de novo” mutations, 27
depression
from brain circuit disruption, 38
and corticosterone secretion, 13
and DBS, 36, 39–42
and glucocorticoid receptors, 30
TRD form, 36, 40–42
and vitamin D, 87
depression-relief circuit in the brain, 40
developmental disorders, 12, 31. See also
childhood abuse and neglect
diabetes, 11, 69
Dicer enzyme, 29
disease-specific data repositories, 12, 15
DNA
and gene protein production, 28
and histones, 2, 21–22
and miRNAs, 14–15
overview, 2
and SNPs, 11, 20–23, 25, 26–27, 31
See also copy number variations; genes
DNA resources of the National Institute of
Mental Health, 4–5
dopamine
and estradiol, 90
and levodopa, 47, 50, 56
and oxidative stress, 52
and Parkinson’s disease, 46–47, 50, 53,
55, 57
pharmaceutical treatments related to,
18, 19, 55–56, 97
and schizophrenia, 11
and urates, 54
dopamine agonist drugs, 55–56
dopamine neuronal toxicity, 87
dopaminergic system, axonal degeneration
in, 50
dorsolateral prefrontal cortex, 24
Down’s syndrome, 24
dysrhythmia, 37–38

E

Early Autism Risk Longitudinal
Investigation (EARLI), 100
Edwards, Scott, 83–92
endophenotypes, 10
environmental triggers
for MS, 62, 63–65
of Parkinson’s disease, 48, 49–50
viruses as catalysts, 6, 21, 63–64, 67
environment versus genetics research, 9–10
enzymes, 29
epigensis, 13
epigenetic regulation of the genome, 2, 3
epigenetics
and behavior, 15–16
and childhood abuse or neglect, 13–14,
30–31
and gene malfunction, 28
overview, 2–3, 13
and suicide, 30–31
epilepsy and DBS, 42–43
“Essay on the Shaking Palsy, An”
(Parkinson), 46
esential tremor, 48
estradiol, 90
estrogens and androgens, 89–91
European Male Aging Study test centers, 89
exercise as neuroprotection, 91
Expert Opinion in Therapeutic Patents
(Alcain and Villalba), 86

F

FDA. See Food and Drug Administration
fear response research, 73–77
fingolimod (FTY-720), 66
Finkelstein, R., 81
Food and Drug Administration (FDA)
DBS approvals, 6, 35–36, 39, 42, 43
and Inderal, 77
on methylphenidate, 80
and natalizumab, 66
and neuroprotective agents, 84
forgetting fear responses, 73–77
Freeman, Walter, 34
free radicals, 47, 52, 84–85, 87, 89. See also oxidative stress
Friedlander, Martin, 96
Frontiers in Neuroendocrinology, 90
FTY-720 (fingolimod), 66

G

GABA (gamma-aminobutyric acid), 11, 29
Gaucher disease, 49
GBA (glucocerebrosidase) gene, 49
genes
  DBS’s effect on, 38–39
  neuronal adhesion genes and ASD, 99–100
  See also DNA; genetic complexity; genetics; risk genes
  “gene silencing” therapies, 28
  genetic complexity
    of autism, 31, 99–100
    of diabetes, 11
    of MS, 62–63
    of neuropsychiatric disorders, 10, 15, 19, 97
    overview, 3–5
  See also risk genes
genetics
  and AMD, 97
  and autism, 10
  environment versus genetics research, 9–10
  Human Genome Project, 4–5, 7, 19–20, 62
  individually-influenced differences and psychiatric illness, 22
  and miRNAs, 14–15
  misspellings in the code, 20–23
  multiple gene involvement in neuropsychiatric disorders, 2, 6, 10
  overview, 6–7
  of Parkinson’s disease, 48–49
  research methods, 3–5
  and schizophrenia, 9
  therapies for diseases, 6, 18–19
  translation of genes into proteins, 28–30
gene-wide association studies (GWAS), 11, 20, 22–23
  genome-wide linkage scans, 22–23
  Geschwind, Daniel, 27, 31
  glutiramer acetate (Copaxone), 65–68
  glial cells, 55
  glucocerebrosidase (GBA) gene, 49
  glucocorticoid receptor gene (Nr3cl), 14
  glucocorticoid receptors in the brain, 13, 14, 30–31
  glutamate, 11, 97
  glutamate receptor activators, 97–98
  Goodman, Wayne, 34, 38, 39–40
  Greenberg, Benjamin, 39–40
  Group Health Cooperative, Seattle, 91
  GTF21 and GTF21RD1 genes, 32
  guanine nucleotide, 20, 52
  GWAS (genome-wide association studies), 11, 20, 22–23

H

Hafler, David A., 63
Hakonarson, Hakon, 26–27, 99
Hauser, Stephen L., 62–63
heat shock proteins (HSP), 84–85
Hensch, Takao, 81
heritability of psychiatric disorders, 3–5, 8–10. See also genes; genetics
herpes infections, 67
high-penetrance genetic mutations, 4
hippocampus
  and androgens, 90
  and BDNF, 85
  and childhood abuse and neglect, 30
  and estrogen, 89
  and schizophrenia, 24
histone genes, 22
histones, 2, 21–22
H.M. (patient with epilepsy), 72
hormones
  corticosterone hormone, 13
  interferon inflammatory hormones, 65
  sex hormones, 89–91
HPA (hypothalamic-pituitary-adrenal) axis, 13–14
HSP (heat shock proteins), 84–85
Human Genome Project, 4–5, 7, 19–20, 62
Hyman, Steven E., 1–7, 19
hypersexuality, 56
hypothalamic-pituitary-adrenal (HPA) axis, 13–14
hypothalamus, 13

I

immune cells (T cells), 60–61, 66
immune system, 21–22, 60–62
immunosuppressive drugs, 65–68
Inderal (propanolol), 76–77
inflammation-related myelin damage, 60
Insel, Tom, 34
interferon beta-1a (Avonex, Rebif), 65
interferon beta-1b (Betaseron), 65
interferon inflammatory hormones, 65
internal globus pallidus, 42
International Congress on Schizophrenia, 97
International HapMap Project, 20
International Schizophrenia Consortium, 22
iron exposure and Parkinson’s disease, 49–50

J
JC virus, 67
Josselyn, Sheena, 76
Journal of Alzheimer’s Disease, 87
Journal of Geriatric Psychology and Neurology, 88
Journal of Neuroscience, 68
Journal of the American Medical Association, 56

K
Kandel, Eric, 72–73
Kanner, Leo, 10
Kan, Yuet Wai, 55
Kazantsev, Aleksey, 86–87
Kety, Seymour, 9
Kindt, Merel, 76
Korenberg, Julie, 32

L
Lamarck, Jean-Baptiste, 13
laquinimod, 66
Lasley, Elizabeth Norton, 17–32
lateral hypothalamus, 43
L-DOPA (levodopa), 47, 50, 56
Lee, Charles, 24
Lee, David, 89
Leustatin (cladribine), 66
Levi-Montalcini, Rita, 84
Levinson, Douglas, 19–20, 22–23
levodopa (L-DOPA), 47, 50, 56
Li, Chenjian, 50, 51
lifestyle choices, 91–92
linkage studies of genome, 4
Llewellyn, David, 88
Llinas, Rodolfo, 38
Lozano, Andres, 41, 42–43
LRRK2 gene, 50
lymphocytes, 66

M
MacDonald, Ian, 97
macrophages (immune cells), 65
major histocompatibility complex (MHC), 21, 22
Malone, Donald, 40–41
Marder, Karen, 49
MassGeneral Institute for Neurodegenerative Diseases (MIND), 86–87
Mayberg, Helen, 41
Mayo Clinic Proceedings, 56
McEwen, Bruce, 89
McGaugh, James, 76
Meaney, Michael, 13–14, 15–16, 30–31
Medtronic, 39, 42
Mellios, Nikolaos, 29–30
memantine for Alzheimer’s disease, 84
memory and brain plasticity, 80–81
building blocks of, 77–79
and DBS, 42–43, 80
fear response research, 73–77
improving with pharmaceuticals, 79–80
molecular emphasis in neuroscience, 6, 72–73
overview, 81–82
reconsolidation process, 76–77
memory storage, biological schematic of, 72–73
Mendel, Gregor, 8
Mendelian inheritance, 8, 48
mental retardation, 26
metabotropic glutamate receptors (mGlur), 97, 98
methylation, 14
methylphenidate (Ritalin), 79–80
Meyer-Lindenberg, Andreas, 22–23
mGlur (metabotropic glutamate receptors), 97, 98
MHC (major histocompatibility complex), 21, 22
microarrays, 19–20, 26
microglial cells, 92
Milner, Brenda, 72–73
MIND (MassGeneral Institute for Neurodegenerative Diseases), 86–87
minimally conscious state and DBS, 43
miRNAs (microRNAs), 14–15, 28–30
mitochondria, 85
mitochondrial dysfunction and Parkinson’s disease, 46–47, 52
Molecular Genetics of Schizophrenia (MGS) consortium, 21–22
molecular processes, 6, 13–14. See also genetics
Molecular Psychiatry, 22–23, 25–26
Monaco, Anthony, 25–26
monoclonal antibodies, 66–67
motor cortex, 46
MRIs of “silent” MS lesions, 64
mRNAs (messenger RNAs), 14–15, 28–30
multiple gene involvement in neuropsychiatric disorders. See genetic complexity
multiple sclerosis (MS)
    brain scans, month-to-month, 59
    debates on cause of, 63–65
    future of treatments, 69
    neuropharmaceutical therapies, 65–68
    overview, 6
    primary-progressing form, 61, 62
    relapsing-remitting form, 61, 62
    secondary-progressing form, 61–62
    stem cell therapy, 68–69
    multiple system atrophy, 48
    myelin and MS, 60, 63–65
myosin Vb molecule, 81

natalizumab (Tysabri), 66–67
National Institute of Mental Health (NIMH), 4–5, 27–28
Nature
    on brain development, 26–27
    on CNVs, 24, 96
    poll on use of memory boosting drugs, 79–80
    on sirtuins, 85–86
    on SNPs, 20–21
Nature Genetics, 22
Nature Medicine, 97
Nature Neuroscience, 30–31, 50
nematodes (c. elegans), 14–15
nerve fiber damage from MS, 67
nerve growth factor (NGF), 84
neuregulin 1 gene, 23
neurexin 1 gene, 12
neurogenesis, 55, 88
neuroimaging and research, 1–2
neuromodulation, 34. See also deep brain stimulation
Neuron, 72–73, 95
neuronal adhesion genes and ASD, 99–100
neuron regeneration, 55
neuropharmaceuticals
    anti-angiogenesis therapy, 96
    antidepressants, 49–50, 97
    and dopamine, 18, 19, 55–56, 97
    immunomodulators, 65–68
    levodopa, 47, 50, 56
    monoclonal antibodies, 66–67
    neuroprotective agents, 84
neuroplasticity, 24, 39, 80–81, 92
neuroprotection
    antioxidants, 47, 52–54, 55
    from lifestyle choices, 91–92
    overview, 6
    proteins, 84–87
    sex hormones, 89–91
    sirtuin enzymes, 85–87
    TNF-alpha, 92
    vitamin D, 54, 87–89
neuropsychiatric disorders
    and CNVs, 12, 25
    DBS clinical trials related to, 35–36
    genetics and, 2, 8–10
    and glutamate receptor activators, 97–98
    overview, 1–7
    viruses as catalysts, 6, 21, 63–64, 67
    and vitamin D insufficiency, 87
    See also schizophrenia
neurotransmitters
    BDNF, 85
    GABA, 11, 29
    glutamate, 11, 97
    serotonin, 14, 18
    See also dopamine
neurotrophic effect of estrogen, 89
New England Journal of Medicine, 40, 67
NGF (nerve growth factor), 84
NGFI-A transcription factor, 14
NIMH (National Institute of Mental Health), 4–5, 27–28
Nr3cl (glucocorticoid receptor gene), 14
Nrf2 glial cell, 55
NRNX1 neuronal adhesion gene, 99
nucleotides
    and CNVs, 24
    overview, 20–21
    SNPs, 11, 20–23, 25, 26–27, 31
nucleus accumbens, 41–42
obesity
  Alzheimer’s disease, 92
  and cognitive ability, 91–92
  and DBS, 42–43, 80
obsessive-compulsive disorder (OCD)
  from brain circuit disruption, 38
  and DBS, 34, 35–36, 39–40
  DBS approved for, 6
Oh, Michael, 43
olanzapine, 98
oligodendrocytes, 61, 64, 68
orthodenticle homeobox 2 (Otx2) protein, 81
oxidative stress
  and Parkinson’s disease, 47, 52–54, 55
  vitamin D versus, 87

Paracquat and Parkinson’s disease, 49–50
parvalbumin cells in the visual cortex, 81
Parkinson, James, 46
Parkinson’s disease
  and alpha-synuclein, 86–87
  animal model for research, 50–51
  and antioxidants, 47, 52–54, 55
  and BDNF, 85
  brain circuit disruption, 37–38
  and DBS, 6, 35–38, 56–57
  and environment, 48, 49–50
  and estrogen, 90
  genetic components, 48–49
  and lifestyle choices, 91
  male/female ratio, 90
  multiple causes of, 46–50
  and neurogenesis, 55
  and subthalamic nucleus, 35
  and toxic-inclusion bodies, 86–87
  and vitamin D, 54, 87
Parkinson’s-like dementia with Lewy bodies, 48–49
Patoine, Brenda, 33–44
pegaptanib, 96
Pericak-Vance, Margaret, 99–100
Perrimon, N., 81
pesticides and Parkinson’s disease, 49
Pike, Christian, 90–91
pituitary gland, 13
PKM zeta enzyme, 6, 72, 78–79
PKM zeta inhibitor, 78–79
plasticity, 24, 39, 80–81, 92
PML (progressive multifocal leukoencephalopathy), 66–67
postmortem studies of human brains, 10–11
post-traumatic stress disorder (PTSD), 30
Prader-Willi Syndrome, 12
precursor miRNA (pre-miRNA), 29
prefrontal cortex and schizophrenia, 29–30
presenilin genes, 19
primary miRNA (pri-miRNA), 29
primary-progressive MS, 61, 62
Prineas, John, 64
Proceedings of the National Academy of Sciences, 80
progressive multifocal leukoencephalopathy (PML), 66–67
progressive supranuclear palsy, 48
propanolol (Inderal), 76–77
protein aggregation and Parkinson’s disease, 47
protein receptors, 96
proteins
  alpha-CaM kinase II, 72, 73–76
  alpha-synuclein, 47, 49, 52, 86
  CCR3 receptor and CNV, 96
  CREB, 6, 71, 73, 76
  in genes, 28–30
  and miRNAs, 14–15
  neuroprotection from, 84–87
  and Parkinson’s disease, 47
  sirtuins, 85–87
  tau, 90
  ubiquitin, 27
PRSS16 gene, 22
psychiatric disorders. See neuropsychiatric disorders
psychoanalytic theory, 9
psychosurgery stigma, 34
PTSD (post-traumatic stress disorder), 30
purines, 52
Ranibizumab, 96
Rapoport, Judith, 27
Rebif (interferon beta-1a), 65
reconsolidation process, 76–77
relapsing-remitting MS, 61, 62
research
  on mutations in neuregulin 1 gene, 23
  overview, 1–7, 18
  on SNPs, 21–22
research methods
  and animal model issues, 50–51, 92
  candidate genes strategy, 11–12
  fear memory deletion, 74–76
genome-wide association studies, 11, 20, 22–23

gene-wide linkage scans, 22–23
heritability research, 9
for HPA axis, 13–14
identifying susceptibility genes, 18–19
neuroimaging, 1–2
PKM zeta and memory, 78–79
postmortem studies of brains, 10–11
resveratrol, 85–86
Retina, 96
rhythm of brain signals, 37–38
riluzole for ALS, 84
RISC (RNA-induced silencing complex), 29
risk genes
of autism, 10, 25–27
of childhood-onset schizophrenia, 27–28
GWAS for identification, 11
and MS, 62–63
of Parkinson’s disease, 48–49
searching for in 1990s, 18–20
SNPs in, 20–23
Ritalin (methylphenidate), 79–80
RNA, 28–30
RNA-induced silencing complex (RISC), 29
Rubenstein, John, 14
Rudick, Richard A., 63–65, 66

S
Sacktor, Todd, 78–79
SAD (seasonal affective disorder), 87
Saldanha, Colin, 89–91
SARMS (selective androgen receptor modulators), 91
Scherer, Stephen, 24–25
Schiff, Nicholas, 43
schizophrenia
childhood-onset form, 27
and CNVs, 12
as disruption between brain areas, 22–23
neural development and, 11
neuropharmacological development, 97–98
and prefrontal cortex, 29–30
research related to, 9–12, 20, 22–23
and working memory, 1–2
Schlaepfer, Thomas, 41–42
Schoepf, Darryl, 97
Schwarzchild, Michael, 51, 52–54
Science, 22, 86
scleroderma, 69
seasonal affective disorder (SAD), 87
Sebat, Jonathan, 12
secondary-progressive MS, 61–62
selective androgen receptor modulators
(SARMS), 91
selective estrogen receptor modulators
(SERMS), 91
serotonin, 13, 18
severe refractory depression, 40–42
sex hormones, 89–91
Sgene Consortium, 22
Shaw, Paul, 94–95
“silent” MS lesions, 64
Sinclair, David, 85–86
single gene knock-out models, 50
single-nucleotide polymorphisms (SNPs), 11, 20–23, 25, 26–27, 31
SIRT1 sirtuin protein, 85–86
SIRT2 inhibitor, 87
SIRT2 sirtuin protein, 86–87
sirtuin enzymes, 85–87
sleep research, 94–95
Smeine, Richard, 55
smoking and Alzheimer’s disease, 92
SNPs (single-nucleotide polymorphisms), 11, 20–23, 25, 26–27, 31
social stimulation and synapses, 95
Sousa, Inês, 26
sporadic autism, 12
Squire, Larry, 72–73
Stefansson, Kari, 22
Stem Cells, 55
stem cells and MS, 68–69
St. Jude Medical, 41
STOC Study Group (Paris), 40
striatum, 46
stroke and deep TMS, 36–37
subgenual cingulate cortex area 25 and depression, 41
substantia nigra, 46, 47, 54
subthalamic nucleus, 35, 40
suicide and glucocorticoid receptors, 14, 30–31
Sukey, Kayt, 45–57
Susan Lehman Cullman Laboratory for Cancer Research at Rutgers, 54
susceptibility genes. See risk genes
Swanson, Sandra, 71–82
Swedish Health Ministry, 9
synapses and sleep, 94–95
synaptic formation in the developing brain, 25
synaptic homeostasis hypothesis of sleep, 94–95

T
tau protein, 90
Tay-Sachs disease, 8
T cells, 60–61, 66
tDCS (transcranial direct current stimulation), 36, 37
teriflunomide, 66
testosterone, 89–91
thalamus, 35, 37–38, 42, 43
thymine nucleotide, 20
TMS (transcranial magnetic stimulation), 36–37
TNF-alpha (tumor necrosis factor-alpha), 92
Toda, Tatsushi, 48, 49
Tononi, Giulio, 94
Tourette’s syndrome, 36, 42
toxic-inclusion bodies, 86–87
transcranial direct current stimulation (tDCS), 36, 37
transcranial magnetic stimulation (TMS), 36–37
transcription factor genes, 14, 28, 32
translation of genes into proteins, 28–30
Trapp, Bruce D., 67–68, 69
treatment-refractory depression (TRD), 36, 40–42
treatment-resistant OCD, 36, 39–40
Treatment-resistant OCD, 36, 39–40
See also obsessive-compulsive disorder
treatment-resistant Parkinson’s, 35
Tsien, Joe, 73–76, 77–79
tumor necrosis factor-alpha (TNF-alpha), 92
Turner, Maria, 93–100
twin studies of CNVs, 24–25
Tysabri (natalizumab), 66–67

V
Valeo, Tom, 59–69
vascular endothelial growth factor (VEGF) molecule, 96
velocardiofacial syndrome, 12
ventral capsule/ventral striatum, 39–40, 41
ventral lateral neuron genes, 95
Villalba, José, 86
viruses as catalysts, 6, 21, 63–64, 67
Vissel, Bryce, 55
visual cortex, 81
vitamin D, 54, 87–89

W
Weaver, Frances, 56–57
weight control, 42–43, 80, 91–92
Weinberger, Daniel, 97–98
Westphal, Christoph, 85–86
Whiting, Donald, 43
Wigler, Michael, 24
Williams syndrome, 32

Z
ZIP compound, 78–79
ZNF8044 gene and schizophrenia, 22, 24

U
ubiquitin protein, 27
University of Manchester, 88–89
urates in the blood, 52–54