

# Restoring BALANCE

One in three individuals will have a major psychiatric syndrome in their lifetime; addiction or depression—directly or indirectly—affects nearly everyone in our society. New treatment approaches are critical to millions of Americans, and progress in molecular science and genetics is bringing about remarkably successful therapeutic strategies.

BY ELEANOR FOA DIENSTAG

**N**OT LONG AGO, PEOPLE WHO SUFFERED FROM depression or addiction—alcohol, drugs, food, nicotine—were regarded as individuals who simply lacked the wherewithal to pull themselves together. Today they are recognized and treated as mental disorders caused, just like other serious mental illnesses, by complex imbalances in the brain's chemical activity.

“Fundamental to all brain diseases we treat,” says Dr. Mark Hyman Rapaport, chair of the Department of Psychiatry and Behavioral Neurosciences and holder of the Polier Endowed Chair in Schizophrenia and Related Disorders, “is the fact that there is an underlying deregulation of brain circuitry. This deregulation can be modified or improved by a variety of different therapeutic approaches that may include drug therapies, somatic (body) therapies, evidence-based psychotherapies, or a combination of these approaches. What we do,” he adds, “is translational behavioral neuroscience.”

In fact, the Department of Psychiatry and Behavioral Neurosciences is a hotbed of leading-edge basic and clinical research ranging from the impact of substance abuse in pregnant women to innovative methods of treating depression.

“Some places have patients so they can do research; we do research so we can improve patient care,” notes Dr. Robert Pechnick, the associate director of Psychiatry Research at Cedars-Sinai.

The burden of substance abuse on the U.S. economy is estimated at a staggering \$414 billion annually\*, more than heart disease, diabetes and stroke combined. The high relapse rate is the chief reason for this astronomic cost and the major challenge faced in drug abuse treatment. “The addicted brain loses its ability to make normal choices,” says Dr. Pechnick. “A smoker, for example, who sees a cup of coffee and immediately craves a cigarette, exemplifies a ‘cue-driven relapse.’” Pechnick is currently testing a compound that blocks cravings and relapse. His goal is



Jeffery Wilkins, MD and research associate Autumn Quiring analyze levels of stress hormones in participants enrolled in addiction research studies.

within reach: to develop a pill that blocks craving.

Stress is the key driver behind relapse. The good news, according to Dr. Pechnick is that, “Although the addicted brain is different, gene therapy and other new techniques give physicians the possibility of reversing the brain.” Pechnick's research, including using new tools, such as DNA microarray technology, to find biomarkers for stress, is providing the building blocks for improved substance-abuse and depression treatment.

“We are doing clinical research on most of the new drug treatments for alcoholism,” says Dr. Jeffery Wilkins, vice chair of the Department of Psychiatry and Behavioral Neurosciences and director of Addiction Psychiatry. Wilkins, who is the holder of the Lincy Foundation/Andrew Heyward-Amy Moynihan Chair in Addiction Medicine,

is well known for advanced treatment in “dual diagnosis” patients: individuals who have substance abuse problems in the context of other mental illnesses, such as depression, anxiety disorder, etc.

Recent breakthroughs in medication for alcoholism, cigarette smoking and pain pill addiction are showing great promise. “For 50 years, alcoholism treatment meant you went to Alcoholics Anonymous and might take Antabuse, and that was it,” says Dr. Wilkins. “Two new medications have been recently approved by the FDA to parallel new understanding of the neuroscientific basis of alcohol dependence.”

“Addiction alters the brain,” explains Dr. Wilkins. “This is something that was discovered very recently. It took three to four million years of evolution for the human species to become what it is today. Addiction ‘hijacks’ that evolution process. Our

ability to survive, to use our memory, our ability to integrate emotions, reasoning, judgment, gets harvested away from family, friends, or work and turned towards drugs. It is extraordinary how that happens—and it is being demonstrated in a variety of research models, and definitely in humans.”

The areas of the brain that get affected by the addiction process are the prefrontal cortex (responsible for thought, reason and judgment), the basolateral amygdala (emotions), the hippocampus (memory), and the nucleus accumbens, which plays an important role in reward, pleasure and decisions.

A new medication with which Dr. Wilkins has been working appears to alter that process. “We have a new understanding of the biology of alcoholism,” he says, “and we have new treatments.” A four-year clinical trial,

\* Source: Substance Abuse: The Nation's Number One Health Problem, Prepared by the Schneider Institute for Health Policy, Brandeis University for The Robert Wood Johnson Foundation, 2001



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in which he was one of the national site principal investigators, demonstrated the ability of a long-acting injectable medicine to decrease relapse. This medication was recently approved by the FDA. “People in this study stopped drinking,” he says.

Since stress plays such a major role in the wheel of relapse, the Addiction Medicine program is also focused on helping addicted patients de-stress without drugs, teaching them meditation and other relaxation techniques. “People do really well with meditation and relaxation,” says Dr. Wilkins. “What is particularly good about these techniques is that, unlike drugs, there are no side effects.”

The next step is to further refine and improve user-friendly aspects of these treatments for alcoholism to make them widely used. “There are about 5,500 addiction experts in the country, and about half a million medical practitioners,” notes Dr. Wilkins. “To treat alcoholism effectively, you need to get the family practitioner, the internist, and ER doctors

linked and supported in some way. Our goal is to have doctors at Cedars-Sinai know how to treat alcoholism or at least know how to work with our group. We are training our staff to learn how to evaluate and prevent alcohol or sedative-hypnotic withdrawal. It is an important issue, because we need to be able to see these problems in patients in order to treat them.”

In addition to making advances in the treatment of addiction, the Department of Psychiatry and Behavioral Neurosciences is developing research models that look at the impact of maternal substance abuse—from alcohol, stimulants, and tobacco—on the offspring. It is also spearheading programs to help prevention among children in middle school and high school. “If a child doesn’t use illicit drugs or isn’t trapped by alcoholism before the age of 15,” says Dr. Wilkins “the chances of having adult addiction problems are dramatically decreased.”

**D**EPRESSION IS A MAJOR PROBLEM FOR over half of the patients seeking help at the Department of Psychiatry and Behavioral Neurosciences. Worldwide, major depressive disorder—characterized by sadness, sleeplessness, fatigue, feelings of worthlessness, and other debilitating symptoms—affects more than 320 million people and is the fourth-greatest source of disability, with a high rate of relapse. Depression often co-occurs with other serious illnesses such as heart disease, stroke, diabetes, cancer, and Parkinson’s disease. Physicians and scientists are working on a broad array of studies that seek to alleviate depression in innovative ways, primarily because about 50 percent of patients do not respond to existing treatments.

Dr. Mark Hyman Rapaport authored a large-scale investigation published in *Neuropsychopharmacology* on the need for long-term, continued augmentation therapy in treatment-resistant depression. Augmentation therapy uses two different treatments that may have different mechanisms of action to create a synergistic treat-

ment response. “The theory,” says Dr. Rapaport “is that there may be different areas of the brain that require different interventions at different points in time in order to effectively influence behavior.”

“What was remarkable with this study was that we found a subset of people who may need a burst of treatment but don’t need continued augmentation with a broad spectrum psychotropic drug to make their antidepressant medication work effectively.”

Treatment-resistant depression is associated with the risk of increased morbidity and mortality and with a severely decreased quality of life. “It is one of the most pressing public health needs that we face as a society,” Dr. Rapaport says. “We are very encouraged by this research, and we hope this study will stimulate other researchers to pursue investigating the need for the continuation of supplemented therapies.”

Dr. Rapaport is also pursuing alternative, non-drug treatments for depression. “The mind and body are intimately connected,” he notes, “and we need to really understand the impact of nontraditional and traditional approaches on what we do, which is behavioral neuroscience.”

He has received National Institutes of Health funding to study the treatment of depression using alternative therapies, such as changing the ratio of Omega-3 (fish oil) to Omega-6 fatty acids in diet and using St. John’s Wort to treat minor depression. He is also investigating the beneficial effects of massage brought about through release of the brain hormone oxytocin.

“We are making real progress,” says Dr. Rapaport. “We are beginning to understand the brain. Thanks to genetics, new research models, and new medications, we have a real chance to make a difference in people’s outcomes.”

## The Genetics of

# E M O T I O N S



What if it were possible to pinpoint the genetic basis of human emotion? Is there such a thing as a gene that evokes compassion? Empathy? Anxiety? Aggression? If so, might this finding spawn new drugs to cure certain psychiatric disorders?

These are queries that absorb Julie R. Korenberg, MD, PhD. Hers are no ordinary ponderings. As a contributor to the Human Genome Project, she is a pioneer in understanding the genetic origins of brain structure and function. Dr. Korenberg holds the Geri and Richard Brawerman Endowed Chair in molecular genetics at Cedars-Sinai Medical Center, where she is director of the neurogenetics division in the Department of Pediatrics. For the past three decades, she has been at the forefront of modern genetics, pioneering the field of human molecular cytogenetics and answering basic questions of genome structure and evolution. Her research has appeared in more than 200 leading scientific publications.

Answers may lie in her groundbreaking, NIH-funded research in Williams syndrome, a rare disorder affecting one in 20,000 people. Those with Williams syndrome are missing no more than 20 genes from one chromosome of the seventh chromosome pair. That minutely small difference in genetic makeup results in heart problems, mental retardation, and characteristic facial features. People with Williams often feel music in a keenly emotional way. Their language is rich and engaging. Experts describe them as genetically predisposed to increased anxiety, combined with hyper-sociability; they have a strong drive toward social interaction.

Over the years, Dr. Korenberg and her team have studied the DNA of more than 300 families with Williams syndrome. Their pioneering work has led them to develop new techniques to identify the location of the missing genes, integrating behavioral testing, human gene sequencing and brain imaging.

In 1999, a colleague introduced Dr. Korenberg to a little girl in the Cedars-Sinai Genetics Clinic who exhibited an unusual form of the syndrome: She was shy. She scored lower on sociability tests than other two-year-olds with Williams. It turns out that she carried at least one of the genes, or a small cluster of genes, that others with the disorder lacked. “These genes appear to modify hyper-sociability, and we identified them,” says Korenberg. “This little girl provided us with a dramatic clue to the influence of genetics on human behavior.”

The implications were powerful. “For a long time we’ve known that the brain circuitry in people with anxiety or depression is somehow deregulated. But we’ve never understood why,” she says. “We also know that certain medications are somehow changing the activity in some brain circuits in people with mood disorders. Yet we do not know exactly why the circuit is faulty to start with, what controls it, what the genetic component is.”

Now Dr. Korenberg and her colleagues have found a genetic gateway into exploring that circuitry and identified the cerebral pathways underlying human emotion and social behavior. “We are incredibly excited,” she says. “We know that if you change this small genetic region, you can affect social behavior.”

Their discoveries may lead to novel new therapies for depression and anxiety and may also help us gain a better understanding of compassion, empathy, and what makes us human.

—IDELLE DAVIDSON