

## Life Without Episodes: Major Depression's Hidden Group

**W**hen **Francis Mondimore** began to interview patients whose first of many bouts with serious depression came at a fairly tender age—before their 30s—he didn't expect this response: They were bewildered.

From his years in the clinic, psychiatrist Mondimore had hunches about lasting depression. But they didn't become truth until he joined the Hopkins arm of a large NIH-sponsored effort to identify genes for recurring major depressive disease. "The Genetics of Recurrent Early-Onset Depression," or GenRED project, operates on the premise that genes for early-striking disease are probably more obvious than later types. As part of GenRED, Mondimore began assessing patients, recording their history, writing comments. And that's when his "interview troubles" appeared.

At fault was the list of standard questions: *When was your most severe episode of depression?* and *When did that episode start? When did it stop?* "Every few patients, I'd get someone who'd look at me blankly and say, 'Episode? I don't know what you mean. There are no episodes; I've been depressed as long as I can remember!' It became clear," Mondimore explains, "that the questionnaire didn't capture everyone's experience. For some,

it's like asking them exactly when friendship stops and love begins."

And meetings when Mondimore and colleagues would read each others' interviews and assign diagnoses became equally troublesome. Of three patients with nearly identical histories, says Mondimore, one would get the diagnosis of a very long single episode of major depression. Another would get labeled with the chronic, low-level symptoms of dysthymia. The third had frequently recurring major depression. "Standard psychiatric descriptions would just fall apart," he says. "On the other hand, if you looked at the boxes on the study's questionnaire marked 'chronic' or 'not chronic,' everyone could agree on that."

Far more than just a relative handful of patients didn't fit standard categories, Mondimore says. Both GenRED and an earlier, respected nationwide study showed that a significant number—as many as a quarter of those with major depression—live with it without much pause for



Frank Mondimore's conviction that his "interview troubles" weren't a quirk helped create the new depression category.

years. "It's not an acute illness for them," he adds.

So Mondimore, colleague **James Potash** and a national team examined data from all of GenRED's 630 families in a new light, picking out only those with the "chronic" box checked. What's appeared is a new, genuine subtype of major recurring depression, one where genes play an intrinsic part, especially if struggles begin before adolescence. Further, they found, these chronic patients are at greater risk of substance abuse, suicidality and panic disorder.

Does knowing all this affect treatment? "Yes," says Mondimore. "For one thing, it justifies not trying to taper some patients off antidepressants. But it also means you re-educate them to view their illness more like diabetes, as a problem to be managed over time. If blood sugar levels jump, for example, you don't ask, 'has the insulin stopped working?' You look at what's going on in a patient's life, at what needs to change to get better control." ■

For information: 410-614-1017.

### TRANSLATIONS

#### Way to Go

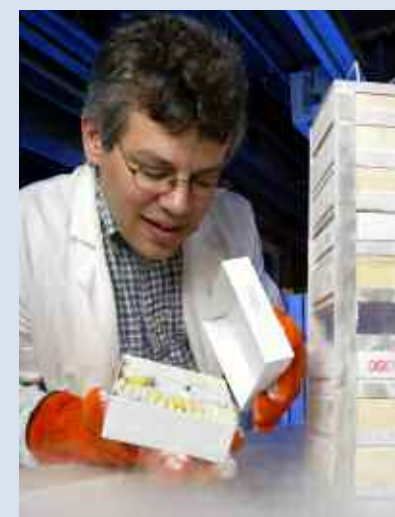
As it begins to sink in that "chronic" is a true variety of major depression, don't expect dramatic change in the way we treat patients, says psychiatrist **James Potash**, senior researcher on the Hopkins team (see left) that teased the finding from a larger study.

"It ultimately helps patients to have more realistic expectations," he adds, "and we remind them of the Hopkins dictum for chronic depression: We aim for you to be 80 percent well 80 percent of the time."

But at this early point, the study's benefits come more as signposts for research. With a "pure" group of chronically depressed patients, says Potash, we're now better able to describe their illness and see what we don't know.

"They're people swimming below the surface," he says, citing a colleague's description. "At times they plunge deep down. At others, they're only inches away from the top. What they have, then, is chronic low-grade depression—dysthymia—with major depression superimposed. Both, we think, are versions of the same thing." But are they? And what causes the plunge? Is it stress? Genes? An unfortunate mix? Some patients are resistant to antidepressants—are the chronically depressed more often in that group?

Finding which gene or genes make depression chronic is the step that would lead to answers for hovering questions, as well as suggest new targets for therapy, Potash says. One gene search is under way—GenRED II—at Hopkins and nationally. The first GenRED sought the broad chromosomal areas likely to harbor depression genes. It kindly uncovered just such a "neighborhood" on chromosome 15. Now with GenRED II about to screen several thousand patients, "we hope to return there," Potash says, "and, in effect, go door to door to pick out specific genes." New-generation gene chips that can scan up to 500,000 variable sites in a patient's DNA "give us a gene-hunting power we never dreamed of." ■



#### Dealing with FTD

It's what we do.

PAGE 2



#### Huntington's Hunt

Closing in on HD helps other diseases.

PAGE 3

#### Accentuate the Physical

Gil Lamphere debunks the myths of depression.

PAGE 4

# Looks Like One, Quacks Like One, Decidedly Isn't

A rare Huntington's look-alike could help the cause.

The irritability, the hours closeted in her bedroom and the mood swings would've been reason enough for the Taylors to bring their sister, Lavinia,\* to a psychiatrist. But in this family, dismay comes before a diagnosis. They've seen their relatives' progressive decline, watched as clumsiness, involuntary movements, odd behavior and thinking take over, and life fades away.

So, in 1995, when family history and a morning of neurological, cognitive and psychiatric exams at Hopkins' Huntington's disease (HD) clinic confirmed their sister's troubles ahead, the Taylors weren't surprised. Psychiatrist **Russell Margolis** and his colleagues, however, were. And that surprise has cleared an unusual path in Huntington's research.

One offshoot of the 1993 discovery of the HD gene mutation was the appearance of a test to spot it in patient DNA, one that Hopkins was quick to include in patient workups. And data has mounted tying those with the disease to the characteristic mutation, a large repetition of a pattern of DNA bases—CAG,CAG,CAG and so on—called a repeat expansion. Researchers

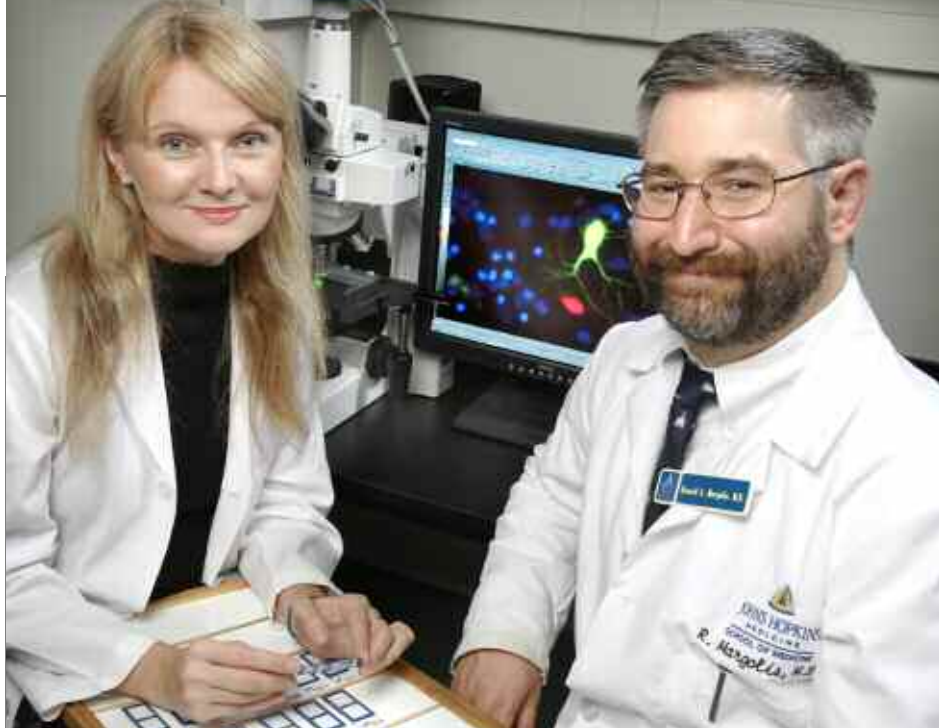
here found that the more repeats, the earlier the onset of Huntington's disease. But nobody has been able to show how repeats lead to sure, irrevocable death of deep brain nuclei. That would be the veritable key to therapy.

Then, however, along comes Lavinia, who turned things around. "We hadn't had any reason to believe she was different," says Margolis. To anyone's clinical eye, the African-American woman in her late 30s had HD; all the neurological, cognitive and behavioral symptoms were there. CT and MR images showed the same brain shrinkage.

But Taylor was negative for the mutant HD gene. Yes, she had abnormally high repeat expansions, but of a different kind, a CTG,CTG pattern. Moreover, Margolis' team found, the culprit mutation was on a different gene, on a different chromosome.

A field trip to the family's North Carolina home told more. "We saw an illness nearly identical to Huntington's visually, but with the key genetic difference only in affected family members," says Margolis, who heads Hopkins' Laboratory of Genetic Neurobiology. He estimates that the new disorder,

"We hadn't had any reason to believe she was different."



"It's taken us years to get this far," says Russ Margolis, whose work with Dobrila Rudnicki shines a light on HD.

called Huntington's disease-like 2 (HDL2), claims less than 1 percent of those diagnosed with HD.

Now the team has identified 25 HDL2 families, many in South Africa. A half-dozen autopsies verify the strong similarities. But despite HDL2's being both incurable and rare to boot, it holds unusual potential to explain HD. "We know it's odd that such an uncommon disease has such importance," says Margolis. "But its HD-like outcome suggests the two share a common pathway at some point—a place to focus our efforts to get at the major mechanisms and to target therapy, if we're lucky, for both diseases."

Led by colleague **Dobrila Rudnicki**,

**Ph.D.**, Margolis' team has begun crucial work to define how HDL2 and HD differ on a molecular level. Already there's evidence that the odd repeats in the DNA spark appearance of a flawed RNA that, by itself, can damage neurons—a new and unsuspected agent of nervous system disease. Rudnicki has shown that nerve cells carrying HDL2 genes don't survive. And direct contact with the abnormal RNA quickly kills nerve cells in cultures. Next, the group begins studies with their newly created HDL2 animal models—a useful result of a family's help. ■

For information, call 410-614-4262.

\*not her real name

## Frontotemporal Dementia: It's Not Knuckleheadedness

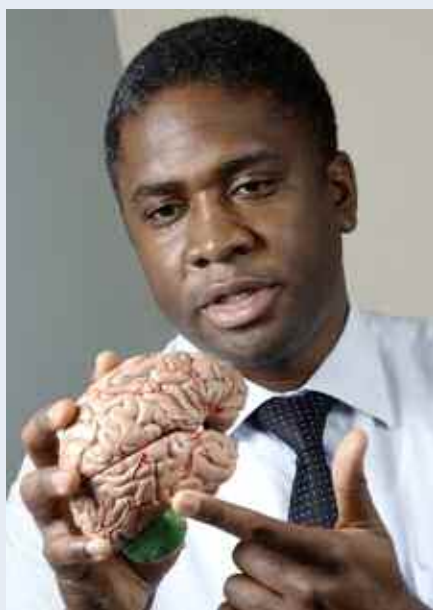
Psychiatrist **Chiadi Onyike** remembers it vividly: A middle-aged woman sat quietly at a dining table and picked up her glass several times for a sip. This went on for some time, says Onyike, yet not a scrap of food had been served. Her plate was bare, her glass empty. "It's the small scenerios," he explains, "that give you a fine sense of frontotemporal dementia (FTD)."

Onyike, who heads Hopkins' FTD clinic, aims to increase awareness of this type of dementia—often wrongly diagnosed as Alzheimer's—as well as spread the word about clinic benefits. "Up to 20 percent of middle-aged patients who seek memory or dementia help have some form of FTD," he says, "but few physicians other than neuropsychiatrists or behavioral neurologists are aware of it."

An umbrella term, FTD covers up to seven fatal diseases—like Pick's disease—all marked

by dementia and atrophy of the brain's frontal and/or anterior temporal lobes. The illnesses can affect behavior or language. The former brings what Onyike calls "a history of social miscues and misde-meanors that patients' families may misinterpret as something psychiatric or as just knuckleheadedness." Uncle George's wanting to wear sweatpants to work seems odd, for example, but it's his rude remarks, his repeated hair-combing and overblown jolliness that cross the line. In the language variants of FTD, patients' speech deteriorates gradually; they become mute. Alternately, those with semantic dementia lose ability to comprehend language.

While the FTD diseases share the anatomy that's under siege, sharp differences exist in pathology. At a cell level, FTD still has no definitive signature, Onyike says. In some of the diseases,



Chiadi Onyike, M.D., M.H.S.

brain cells carry telltale tau or beta-amyloid proteins; others may display different inclusions or none at all, apparently. Even when FTD results from a known gene—some 40 percent is familial—there's puzzling variety, he adds. "Members of one family

can have different types of FTD."

"The complexity gets in the way of research and of educating people," Onyike explains. It can also slow diagnosis, though at Hopkins, clinical expertise usually wins out. Patients, with their caregivers, initially spend two to three hours at the clinic, giving a detailed history and undergoing cognitive and neurological testing. Brain imaging and EEGs may also be scheduled.

Clinic staff additionally assess home safety and driving competence. "Driving problems, by the way, don't typically involve forgetting where you're going," says Onyike. But with advancing FTD, attentional skills may change for things like timing oncoming traffic. "When judgment lapses, patients can resemble inexperienced, reckless teenagers behind the wheel."

The clinic provides a prognosis, aims for a safe environment, educates families and helps them anticipate future care, legal and financial issues.

Because there's no cure, a certain mindset defines the place. "One needs calmness and ability to accept things as they are, not as you'd have them," says Onyike. Perhaps this comes from his growing up in Nigeria or attending medical school there years before he came to Hopkins. "I never knew the main role of medicine as providing a cure. I came to know it as providing clarity, comfort and guidance and, if you're fortunate, a cure. If a cure's available, you only walk a short way before you and patients shake hands. With FTD, you walk a longer distance, sometimes the whole way, with the family." ■

For information, call 410-502-2981.

# The Hunt for Huntington's

*HD's still a black box; the search for a way inside is changing psychiatry.*

*Woody Guthrie had it.*

*It gives you ceaseless, jerky movements.*

*It's fatal.*

*That's what most people know or want to know of Huntington's disease—even some clinicians.*

*Christopher Ross didn't have such a tight grasp on HD, either, when he came to Hopkins as an intern two decades ago. But seeing patients in the clinic set up by mentor Marshall Folstein rooted an interest.*

*Why would a young psychiatrist take on what's overtly a movement disorder and chip at it for years so that it becomes a defining work? For one thing, HD patients suffer an asylum-full of psychiatric disturbances: apathy, depression, obsessions, psychosis, substance abuse, paranoia. Cognitively, they slip from problems with planning and other executive functions to frank dementia. All—so far—without a cure. For Ross, the lure was the possibility of understanding HD's biology. Huntington's is strongly genetic, its symptoms clear. And Ross was ready, having completed an M.D./Ph.D. program in neu-*

*rosience, then Hopkins postdoctoral training under hallowed neuroscientist Sol Snyder. When insiders knew the HD gene would soon be found, Ross made his move.*

*Now the director of Psychiatry's neurobiology division and head of its Huntington's Disease Center—possibly the world's largest HD clinic—Ross has been in the thick of work that's greatly advanced our understanding. His team developed techniques to detect HD's novel type of mutation and show that its "severity" matches the disease's onset age. Using the human HD gene—it codes for the mutant protein huntingtin—he's created cell cultures and an important mouse model to test therapies. His group identified huntingtin; now they're defining its abnormalities. They've suggested how the protein may disrupt gene expression in affected brain cells. Most interesting are ways they've found to slow the disease in the animal models—clues for potential therapy.*

**Q.** The HD gene surfaced in 1993, but there's still no remedy.

**A.** We had no idea how difficult

it'd be to find how huntingtin kills nerve cells. Still, our progress is real: We know huntingtin's cleaved into smaller molecules that aggregate inside cells. We know it triggers a host of toxic responses downstream and precisely what they are. We just need the intermediary steps. And we're checking places to intervene—that first cleavage, for example. If an enzyme causes it, there's a drug target.

**Q.** How could drug companies not be interested?

**A.** They are now! They used to think the market was too small. But that's changing.

**Q.** Why?

**A.** Because Huntington's resembles Parkinson's and Alzheimer's diseases in major ways. So if we find an HD treatment, something should be there for the other illnesses. Pharma knows that.

**Q.** Any possible therapies?

**A.** Two antidepressants, surprisingly, look interesting. Sertraline (Zoloft) slows brain shrinkage in our model



mice. Paroxetine (Paxil) appears to do the same, partly by increasing the growth factor BDNF in the brain. We're hoping clinical trials could be down the road.

**Q.** Do we have a strategy for HD?

**A.** Our plan for now is to delay its onset as long as possible by combining approaches. That means we must catch patients before their symptoms develop—damage begins some 15 years before diagnosis is possible. So we're actively seeking good predictors in people with the gene, things to tell us when to start treating.

**Q.** What sets us apart?

**A.** We use the most advanced molecular and cell biology techniques, along with mouse genetics, to tackle clinical problems. That's not so common in psychiatry departments. ■

## Autoimmune Disease, Thought and Mood

Our lab is studying the effects of autoimmune neurologic diseases that are associated with depression and difficulties in memory and/or concentration. **Specifically, we're looking at effects of cytokines—the immune system's chemical messengers—on the brains of patients with transverse myelitis (TM) or multiple sclerosis (MS), comparing them with each other and with those who have non-autoimmune myelopathy.** The prospective study (with a 6-month follow up) involves measuring cytokine levels and mood, cognition or neurological status. Participants age 18 to 65 and diagnosed within the last three weeks with TM, MS or non-autoimmune myelopathy are eligible for this study supported in part by the Dana Foundation. Adam Kaplin, M.D., Ph.D. leads the investigation. Participants are paid for the study. Call 410-502-2574.

## Bipolar I/Bipolar II

**Currently depressed patients with bipolar I or II disorder may participate in a trial of the medication Riluzole.** While Riluzole is used to treat ALS (Lou Gehrig's disease) because it appears to lessen availability of the neurotransmitter glutamate, the drug may also have nerve-protective properties that may be helpful in relieving depression. Participants must be between age 18 and 75 and already taking a mood stabilizer. They'll be tapered off any present use of antidepressants. The study lasts eight to 12 weeks and involves an initial screening visit and weekly visits to Hopkins thereafter. Half of those in the study are randomly chosen to receive Riluzole; the other half is given a placebo (sugar pill). Participants are paid for the study. Jennifer Payne, M.D., is the principal investigator. Call 410-502-2334.

## Parkinson's Disease and Cognitive Impairment

Investigators at the Johns Hopkins hospital seek **volunteers with Parkinson's disease**, older than age 50, to participate in a research study funded by Forest Pharmaceuticals. If you have difficulty with your memory, you may qualify for this study. Laura Marsh, M.D., is the principal investigator. Call 410-614-1242.

## Obsessive Compulsive Disorder We're interested in studying how children and adolescents ages 6 through 17, either with obsessive-compulsive symptoms or without them, function within their families.

The study occurs in the home; no hospital or school visits are necessary. We conduct a phone interview with parents to discuss a child's behavior and daily functioning as well as the parent-child relationship. Paper-and-pencil questionnaires are given on various aspects of family functioning.

Children or adolescents also participate in a phone interview regarding behavior and daily functioning. They, too, fill out questionnaires on the parent-child relationship and on personality. When participation is finished, children are given a \$15 gift certificate to a book store. Marco Grados, M.D., M.P.H., is principal investigator. Call 443-287-2291 or e-mail mjgrados@jhmi.edu.

## Schizopolar? Biphenic? Why Boundary Blurring May Help



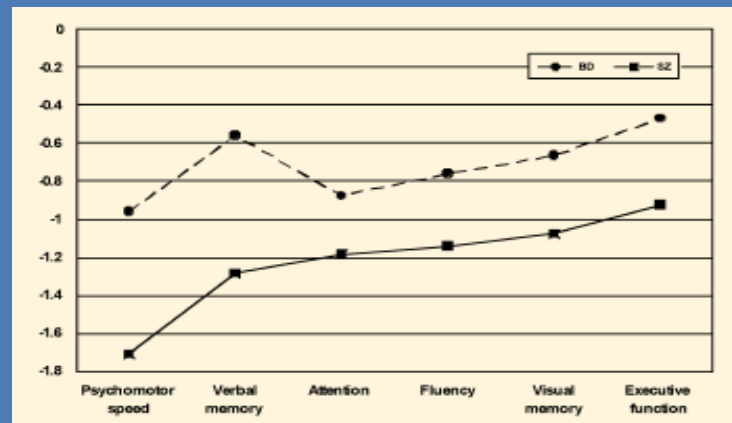
When, in the late 1800s, German psychiatrist Emil Kraepelin pointed to dementia praecox and manic depressive psychosis—now schizophrenia and bipolar disorder—as distinct diseases, he wasn't blind to some overlap

between the two. Psychosis marks both illnesses, of course. Their numbers are roughly the same, population-wise; they're close in onset age. They strike both sexes similarly. Kraepelin, however, was looking at overall symptom patterns. And for a century or so, his distinctions have driven diagnosis, therapy and research.

overlap both illnesses as a way to tie symptoms to specific genes. As a bonus, he may find just how much biology schizophrenia and bipolar disorder (BD) share.

"Subtypes exist; we know that," says Schretlen. In some schizophrenia patients, for example, delusions stand out; with others, it's hallucinations. Or negative symptoms can rule—apathy, emotional blunting, not wanting to wash or talk. Likewise, he adds, some bipolar patients become psychotic in acute disease; others don't. Mania can overshadow depression. Or not.

"Perhaps we need to set diagnostic labels aside," he says, "and look at both illnesses instead in light of, say, the presence of psychosis or severity of mood symptoms or even the nature of cognitive losses." Lately, Schretlen's been focusing on that last one. His multi-center team has begun by getting a



baseline of cognitive abilities in the two disorders. Recently, they gave 106 schizophrenia patients, 66 BD patients and 316 healthy adults unusually wide-ranging tests of cognition—attention, concentration, memory, reasoning, visual perception, processing speed and the like. This early work deserves kudos for overcoming the classic obstacle to studying cognition in these disorders, namely, the way that age, sex, IQ and other demographics skew results. "Bipolar patients, for

example, are often so far above average intellectually that they can mask their cognitive problems." So, he uses statistics to level the field.

Schretlen found that both illnesses harm patients' thinking, though it's more intensely so in schizophrenia (see graph). Surprisingly, the kinds of problems in schizophrenia and bipolar disorder almost parallel each other. "That," says Schretlen, "suggests common biology." ■

For information: 410-955-3268.



## Sallie Mink: Psychiatry's Clear Voice

Shortly after her talk on depression at a local high school, **Sallie Mink** got a call from a woman in distress: "My son handed me one of your brochures this morning. He said he's kept a knife under his pillow for two months, waiting to see if things got any worse. I don't know why. I don't know what to do. We're good parents."

Mink, a psychiatric nurse by training, called on hard-won insights—ones that've come since the mid-1970s when she arrived

"I tell anyone who'll listen about the healing power of skilled therapists," says Mink.

at Hopkins—to shape her reply. "People were convinced that most mental illness was rooted in poor parenting," Mink says. And that enhances the stigma of having a mind disorder, one, she adds, "that's still sharp today."

Now, as Psychiatry's nurse coordinator charged with education, Mink fights all that. She matched mother and son with a clinician specializing in teens' mood disorders. But she also worked to reduce the mother's anxiety. "We're reassuring, but honestly so, to the families as well as patients. Anxiety is married to depression, and sometimes," she says, "it's all people can do to call us. When they do, they sure don't want voice mail."

In teaching local civic, faith or school groups or in acting, in her words, "as a go-to person" for prospective patients, Mink also destigmatizes. "I emphasize the genetic basis of depression," she says. "I remind people that it's an illness, not a result of weak character. People don't always believe me at first. You have to keep at it."

Mink's start as a psychiatric nurse in the then-Phipps Clinic evolved into community outreach, with 20 years with the Depression and Related Affective Disorders Association, a regional patient awareness group founded by psychiatrist Ray DePaulo. She's planned and run DRADA's hugely popular yearly symposium, an event she still organizes, though now it's under the Department of Psychiatry and Behavioral Sciences, where she works today. Mink's overtures to high schools, begun years ago with equally passionate Psychiatry faculty, have blossomed into ADAP, a depression awareness program for teens, now on the verge of going nationwide.

For information: 443-287-3480.

ON MY MIND: GILBERT LAMPHERE

## Put Together Again

*How the king's men mended Gil Lamphere's depression.*

*Last June, a fact-finding House subcommittee on health listened intently to Gil Lamphere, a New Yorker with enviable business savvy. Lamphere has a Forbes profile. He's directed several companies, including the Canadian National Railway. Now he's managing director of a thriving private equity firm, a man with the electric sort of insight you'd expect of someone who's done so well. And he's no stranger to Hopkins.*

What is not on my resume is that I was severely depressed for three years. In fact, I was in the 99th percentile of severity. I had the finest psychiatric attention my fortunate wealth could access. I had tried 27 medicines, not including combinations. I had 42 shock treatments. I spent 20 weeks in and out of hospitals. I lost my loving wife to divorce six months prior to the end of my successful treatment. I lost my family, a good deal of my assets, my apartment, my job.

Finally, when the last shock treatment series had failed, a friend said: Get to Johns Hopkins. There I was told I'd be lucky, given my severity, to regain 80 percent normalcy 80 percent of the time. But since normal for me is more like 120 percent—not manic, just happy and energetic—I told Drs. **Raymond DePaulo** and **Paul McHugh**, two world-class psychiatrists, that wasn't good enough. Just pull out the stops, I told them. Worry about side

effects later. So they thought outside of the box, as they do. In fact, they collapsed the box entirely.

Hopkins gave me a 30-year-old, off-patent antidepressant called Parnate, an MAO inhibitor invented in the 1970s, together with Geodon, a new drug designed to calm hallucinations in bipolar disorder and schizophrenia. Hopkins discovered it has powerful antidepressant effects at low dosages. Add to the mix lithium and Lamictal as antidepressant mood stabilizers and I had the perfect cocktail. I spent 12 weeks off and on at the hospital. Here we are, two and a half years later, and I feel better today than ever in my life.

Against this backdrop, I have two points to make. First, depression and bipolar disorder are not *mental* illnesses. They are *physical*, in both cause and treatment. I know. In the middle of my illness, my doctor said that part of my brain affecting emotion and cognitive behavior wasn't functioning at all well. I didn't believe him. I knew my thinking was fine: that nothing *was* humorous, *nothing* gave pleasure, and people going to work in the morning *were* like ants with no brains—a repetitive tragedy. At NYU hospital, they hooked up my head to electrodes and recorded. Then I looked at the printouts, prettier than a Christmas tree. My brain's right front blinked red; the back right, green, and so



forth. But—holy smokes—the left front was black with nothing going on.

Mental illness is physical, like diabetes. And if these disorders are thought of correctly, as physically caused and physically cured, mental illness will be acknowledged as a problem in brain biology. The stigma will melt away. Incidentally, I find this insight most accepted by people younger than 60, and less so by older men who feel that if you're depressed, you should "pull yourself up by the bootstraps."

My second point is that finding the right medicines can be drawn out. We understand some of what we're trying to stimulate in the brain, and drugs are targeted to do that. But it's still hit or miss. Medicines can take a long time to work fully; patients grow discouraged that they're not getting better. So we have a physical ailment that can be difficult to treat, that can take time. Thank God I had my family for much of that time and my wealth to get me through. How other people struggle through months and years without human support and the finest sort of care is beyond me. ■

## BrainWise

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**Save the Date!** The 21st Annual Mood Disorders Research/ Education Symposium features award-winning authors and authorities on depression and bipolar disorder Kay Redfield Jamison and Fred Goodwin.

**Tuesday, April 24, 1–6 p.m. at Hopkins' Turner Auditorium**

For information, call 443-287-3480.

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