BrainWise

JOHNS HOPKINS MEDICINE

Spring/Summer 2007

News from the Johns Hopkins Department of Psychiatry and Behavioral Sciences

VOLUME 3, NUMBER 2

ECT Without the Hollywood

After her therapy was finished, Lorrie Nottingham felt enough like herself to let ABC producer Richard Chisholm tell her story. Her filmed experience is a far cry from Jack Nicholson's.

Lorrie Nottingham and Jack Nicholson have little in common, fortunately, aside from the topic of electroconvulsive therapy (ECT).

As a man pushed into "shock treatment" in *One Flew Over the Cuckoo's Nest*, Nicholson brought his too convincing acting to what was a bogus take on the therapy as it had existed in the 1930s. That, plus the film's showing a lapse of medical ethics so staggering that you pray it's fiction, planted the thought in a generation of Americans: *Avoid ECT, no matter what.*

Patient Nottingham, however, is the reality. Last May, the soon-to-be-grandmother became one of the 130 or so each year to undergo ECT at Hopkins Hospital. Unlike the movie portrayal, she was neither in pain nor made a zombie.

"We're well aware of public perceptions," says psychiatrist **Irving Reti**, who directs Hopkins' ECT service. "But what we see is a therapy that works amazingly well for selected patients." Roughly 85 percent of resistant depressions lift with ECT, making it psychiatry's most effective treatment for the illness. "It's not without considerations," he says—like memory loss that's temporary in most—"but, still, ECT is overwhelmingly safe."

For the better part of 20 years, Nottingham has lived with deep depression. "I've had so *many* different antidepressants. They work a while, then stop," she says. And her recent downturn was especially grim; when she came to Hopkins, she lay in bed, tearful, knees drawn in: a human knot of sadness. "I have no future," she'd whisper.

At each treatment session, with both psychiatrist and anesthesiologist present, Nottingham experienced short, barbiturate-induced anesthesia, received a muscle relaxant and then the brief pulse of electricity that induces a seizure. Time asleep: less than five minutes. By the fifth session—most patients have six to 12 over several weeks—she'd become both engaged and engaging.

"I'm much more social," she said, perched on the side of her bed. "I talk to people at dinner. I'm feeling good. I can't describe how, but I am."

Reti and his colleagues share Nottingham's puzzlement at how, exactly, a seizure lightens mood. The going idea is that it turns on specific genes that sculpt brain synapses, and clinician/neuroscientist Reti has spent a decade investigating what regulates this rapid synaptic remodeling. Though much of Reti's work applies to addiction, he says it's not hard to imagine that repeated ECT might tap some of the same genes and share brain circuits. "Also, we know that antidepressants and antipsychotics activate those genes, though with ECT, they're expressed far more robustly." Perhaps that's why the latter acts faster than antidepressants—in two to three weeks or less.

It's still a mystery why ECT's benefits fade in a few months without additional antidepressant therapy or maintenance ECT. Nor is it clear why a drug that had little effect before ECT is one that can keep mood on track afterward. "We'd love to find out," says Reti.

Nottingham, however, is untroubled by thoughts on the mechanism: "I just know it works." ■

For information, call 410-955-3246.

TRANSLATIONS

A Rose by Any Other Name

"I'd never sell ECT as a panacea," says Ray DePaulo, "but I couldn't be a depression-treating doctor without it."

Hopkins Psychiatry Director DePaulo and colleagues know the dilemma of electroconvulsive therapy. They regularly witness the changeover, seeing patients with "incurable" depression—those severely suicidal or psychotic or rigid in catatonia's hard shell—assume a fully normal life. "It's more than that," says DePaulo. "More than a few come to see life as a blessing following ECT." But, he adds, "we've also all seen patients who lose memories and become distressed, especially if they're not prepared."

So ECT is a rose that's sometimes thorny. Keeping a close watch may mitigate the barbs, however, and plays a part in Hopkins' high benefit-to-risk ratio. So electrodes are positioned to minimize memory effects. Current is pulsed rather than continuous. Experienced eyes monitor vital signs and length of seizure. The patient population is select, making ECT far from routine.

As important, transparency must mark dealings with patients and families, says DePaulo. "You insist that family is involved. You lay out the good and the bad, from anesthesia risks to muscle aches to the delirium as you come out of it. And of course, you fully describe and answer questions about cognitive and memory risks, most patients' greatest concern."

For a few months afterward, he says, memory for facts, events or names learned around the time of ECT is typically lost. Recall of events before the treatment and absorbing knowledge afterward can waver. The latter typically resolves in jumps over the coming weeks or months, such that, as a rule, the ability to learn and remember entirely recovers. "Still," DePaulo says, "there's no absolute wall of protection; past memories can be permanently lost."

That's why research is key. Could knowing ECT biology show how to deliver its benefits without the risks? "That's the goal," says DePaulo. ■

Schizophrenia Wisdom for Hire: Consults Without Borders

The fact that Lisa Tucker's diet consisted entirely of eggs, green grapes and hot dogs wouldn't have been such a problem except, asked to prepare meals as part of her group home duties, she refused to serve anything else. If housemates complained or she was pressed to comply, she'd burn herself with a frying pan.*

Tentatively diagnosed with schizophrenia some 20 years ago—there were hallucinations and unrealistic suspicions—Tucker left college and drifted from job to job. Her eating disorder, bound by rituals, became more ingrained with age. And though she now has the support of an able psychiatrist, a psychosocial day program and the staff of her group home in Washington, D.C., "all of them were stymied by the way her odd eating habits and recurrent burns colored her schizophrenia," says Hopkins psychiatrist **Russell Margolis**. "Should they be more confrontational? Less? They couldn't tell," he says. And that uncertainty was reason enough to have Tucker seen at Hopkins' inpatient schizophrenia consultation service.

Three graces with a watchful eye: Observations by nurses Terry Goodwyn, Beth Kuhl and Karen Abernathy on the schizophrenia unit give a reality check.

Even before Margolis became head of the hospital's schizophrenia program last year, he saw a need for broader-based consulting for patients like Tucker. "Schizophrenia is heterogeneous and complex. Its onset alone can mimic other disorders, and symptoms are so variable that early diagnosis is often difficult." That's especially true in a setting of substance abuse or certain personality styles or a fractured home life, not to mention other medical illness.

"Should they be more confrontational? Less?"

With the consults, what Margolis had in mind was a service for local, national and international patients that mirrors the holistic approach firmly rooted in Hopkins psychiatry. Encouraged by E. Fuller Torrey, a worldwide advocate for schizophrenia patients, and colleague **Nicola Cascella, M.D.**, who now co-directs the resulting service, Margolis put ideas to practice.

So Hopkins consultants first search for alternate diagnoses—delusions and hallucinations, for example, occasionally have a curable cause in infection or a tumor. Psychiatrists and nurses probe for personality strengths and weaknesses, suggesting ways to play to strengths. And because patients' life experiences can't help but affect how they view their illness, a sharp awareness there shores up the treatment plan.

Tucker's experience is typical. During her weeklong hospital stay, an MRI, EEG and a battery of blood tests ruled out complicating disease. Staff followed the paper trail on her hospitalizations and called for other useful records. Five faculty experts in schizophrenia or eating disorders talked with family and past care providers. And Tucker, of course, was interviewed many times.

What nurses on the schizophrenia unit saw was an extremely anxious woman. Even under mild stress, her symptoms would snowball to the point where she'd threaten self-harm. But, the nurses found, Tucker could be easily distracted and calmed if she wasn't pushed. Meanwhile, neuropsychological tests revealed a trouble with problem solving that matched what the occupational therapist saw. Tested for ability to carry out real-world tasks, Tucker could follow only one-step directions: No wonder she roused complaints in her group home.

Advice on Tucker's care involved shifts in medicine, changes in her environment and new behavioral techniques to damp her urge to hurt herself. And all agreed she was a prime candidate for an eating disorders program. "At the end," says Margolis, "everyone took home something substantial." ■

**For patient privacy, her name and some facts are altered.*

For more information, call 410-955-5104.

Infant Autism, A Closer Look at Bipolar Psychosis, Smoking and the Workings of an Anti-Alcohol Drug

Early? Later? When ASD Surfaces

Young children who develop autism spectrum disorders (ASD) apparently fall into two distinct groups early on: one that shows clear signs of the problem by 14 months and another that doesn't until 24 months. **Katherine Holman, Ph.D.**, presented those results, at a recent Hopkins Psychiatry seminar, from a study of developmental progress of 125 infants—both little ones at low genetic risk for ASD and others who, because of affected siblings, were at high risk. The research team analyzed reports from parents and home videotapes, noting benchmarks of social, communication and play behavior especially vulnerable in children with ASD. Worldwide, diagnosis typically doesn't occur before age 3. This study may help move it earlier, when interventions could lessen the severity of the disorder. *In press, the Archives of General Psychiatry*.

The Bipolar/Schizophrenia Overlap: Getting Closer

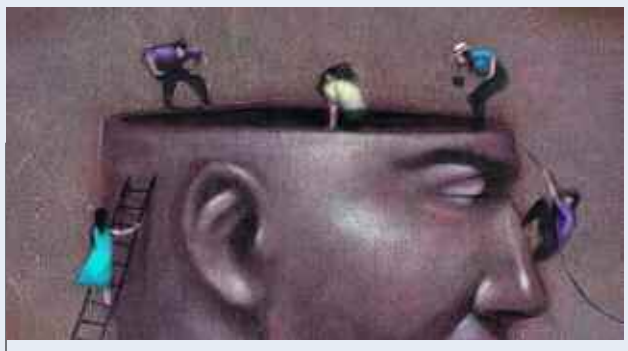
Psychotic thinking in severe depression or bipolar illness isn't rare. And among patients with it, some 40 percent have thought altered in a way that's atypical for mood disorders—like believing their thoughts are being broadcast so others can hear. Recently, a Hopkins-based study of 708 families with bipolar illness compared patients with mood-incongruent psychosis (MICP) and others whose thinking, though typical of psychosis, was in line with usual themes in depression or mania. A research team led by **Jimmy Potash, M.D.**, found MICP patients more severely ill. MICP also clusters more strongly in families than other bipolar groupings. Most important, genetic linkage studies uncovered sites on chromosomes 13 and 2 tied to MICP—especially useful because they match regions previously singled out in patients with schizophrenia or with an apparent schizophrenia-bipolar overlap. *American Journal of Psychiatry*, February 2007.

Schizophrenia: Genes and Germs

Schizophrenia, the latest thought suggests, arises from an interplay of genes and environment. But, so far, there's no proof. Now that several schizophrenia-likely genes have surfaced, however, researchers can use them as a tool to troll for environmental effects. In what may be the first of such work, researchers in the lab of **Mikhail Pletnikov, M.D., Ph.D.**, report devising cell and mouse models that reveal something "outside" could interact with a candidate gene. As **Olga Nikolskaia, M.D.**, told a Hopkins audience, the team created cultures of neuron-like cells, each carrying a mutant form of the DISC-1 gene responsible for the disease in a large Scottish family. When exposed to the common Herpes simplex virus, an unhappy synergy occurred and cultured cells with mutant DISC-1 failed to develop properly. In ongoing studies of mice with mutant DISC-1—under infection-mimicking conditions—the animals will be screened for abnormal brain wiring and behavioral changes.

Smoking and Naltrexone: Strange Bedfellows

The tie between alcoholism and opioid receptors in the brain's reward



system is strong, so much so that researchers suspect that individual receptor types—called mu, delta and kappa—may have starring roles in different aspects of alcoholism.

A recent study of newly abstinent people explores the workings of naltrexone, a medication that reduces alcohol craving and drinking. Their PET scan images showed, first, that in the FDA-approved dose, naltrexone fully occupies their mu receptors—something apparently tied to its helpful effects. But their delta receptors get only partly occupied, and that varies greatly among study subjects. Researcher **Elise Weerts, Ph.D.**, suggests the variability explains why naltrexone works better in some than others. But what might account for that? It's not how long someone's been addicted or the other usual suspects, Weerts says. But it might be smoking. People with a stronger dependence on nicotine had greater delta receptor blockade. "So smokers," she says, "may be helped more by naltrexone." *Neuropsychopharmacology*, May 2007. ■

Bloom Where You're Planted

For early Alzheimer's, staying home could be a matter of the right fertilizer.

Constantine "Kostas" Lyketsos *was born in Greece.* ***Deirdre Johnston*** *drew her first breath in Ireland. It's no coincidence that two psychiatrists born to cultures steeped in social service, ones that hold old people in high regard, find themselves together on a project that aims to rattle the status quo of the at-risk elderly in this country.*

Specifically, Lyketsos, Johnston and other dementia experts are in the midst of MIND—for maximizing independence—at Home. The much-needed study, which makes partners of Hopkins and the Baltimore Jewish community, taps 30 years of research that Lyketsos and Hopkins colleague ***Peter Rabins*** *conducted on identifying and treating patients with early Alzheimer's or other dementias. The project holds to the mission of the Copper Ridge Institute, a research body Lyketsos helped create, to spread its model of care worldwide.*

In MIND's first phase, staff phone-surveyed Northwest Baltimore's older, Jewish population. Phase II is now casting the nets wider to find elders more severely at risk. The study's trained gatekeepers flag potential memory disorders for the project's geriatric psychiatrists. Soon, 300 people with clear, early-stage dementia will enter a controlled trial, to see how care as usual compares with living under the Cadillac of "best practices." At its finish, MIND at Home should stand as a prototype for communities, letting them find and nurture the elderly in early dementia, without plucking them from their homes.

Johnston, the lead investigator, directed geriatric psychiatry at Canada's University of Alberta in Edmonton. There, she helped town leaders create an unusual citywide program for the aged at risk. More recently, she set up a highly effective project of at-your-door medical outreach to homebound elders in neighborhoods around Wake Forest University.

Lyketsos now heads Psychiatry and Behavioral Sciences at Hopkins Bayview.

We shudder at the figure: By 2050, Alzheimer's disease will quadruple worldwide. That's what prompted this project, yes?

(Kostas) That drives it, of course. But specifically, we're doing MIND because of scale. We already know how to give patients with early dementia good care. We just don't know how to make it available to large groups. (Deirdre) Services are available, but often, because dementia comes slowly, people don't realize they need them. And even if they do, driving into Baltimore doesn't work with dementia.

So the idea is that early dementia patients can do better at home?

(Kostas) The theory is: Meet patients' needs and you reduce symptoms. Reduce symptoms and they function better. Then everyone's happier. Patients can stay longer at home. Cost is less. So you structure their day and fine-tune medicines—at home. Not shuttling them around, we think, will make a difference. Just the stress of a cold, for example, can push dementia patients into a really bad patch.

Why have you singled out Baltimore's elderly Jewish?

(Deirdre) Basically because there's wonderful infrastructure. The Associated Jewish Charities, which funded this study, also kindly offered us their telephone lists, demographics and more. We've already cold-called everyone over 70 in three target ZIP codes, given 283 cognitive status interviews by phone, then followed up with 43 in-home visits: Are you on medication? Is the dose right? Are caregivers coping? Sleep OK? The survey we gave was broad and accurate and, fortunately, it led to a simple instrument that others can use to guide at-home care for people with dementia.

Any surprises so far?

(Deirdre) Yes—how frequently family members are overwhelmed. Also, calls aren't enough. We suspect there's a huge vulnerable population out there not picking up the phone. MIND's biggest impact could be on them. ■

SUPPORTING THE CAUSE

To Repair the World

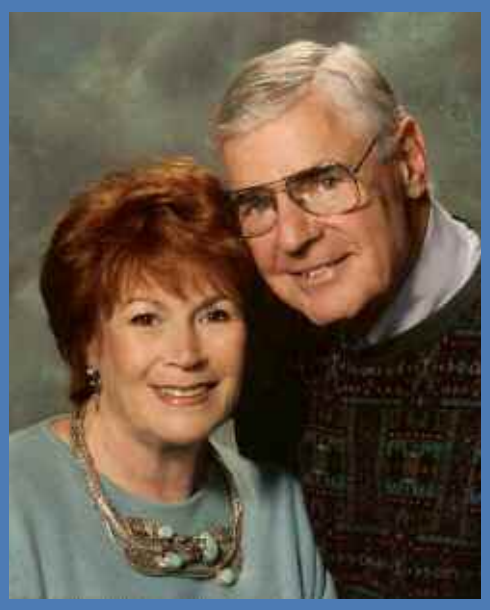
Lillian Stempler was in her mid-60s when a Hopkins visit revealed her Alzheimer's disease. She lived another 20 years. But there's at least one bright spot: The rallying of the Stempler family in the face of all that followed has continued as strength of a different sort. Over the next two decades, two generations of Stemplers have helped shine light on the best ways to treat those with Alzheimer's, not only underwriting the research of psychiatrist Peter Rabins but also encouraging others to do the same.

The family's story is a lesson. The capable running of his Maryland-based uniform company left founder **Oscar Stempler** financially comfortable, so when his wife fell ill, explains daughter-in-law Deana, "he could afford, thank God, to keep her with dignity." Stempler insisted on caring for his wife at home. Yes, the CEO had someone stay with her by day, Deana explains, but "he still went through everything you could imagine." He was the sole caregiver at night, bathing and dressing his wife, taking her to dinner while she was able.

And the rest of the family stepped in. Son Jerry and his wife, Deana, were a constant support, regularly having the elder Stemplers to dinner, tailoring their visits to Lillian's fading abilities. "We had to cope as a family," says Jerry, "and we did our best."

It was shortly after the diagnosis that Oscar Stempler set up an endowment for dementia research at Hopkins. Later, after Jerry took over as CEO of the family company—seamlessly, many said—he, too, nurtured a calling for *tikun olam*, Hebrew for "repairing the world."

"It's not just something you say for an interview," says Deana. "We feel blessed that this research is going on. We can't wait for this disease to be eradicated." ■



Deanna and Jerry Stempler

RESEARCH'S ROAD

Addictions

Are you currently addicted to heroin or prescription pain relievers? Are you seeking treatment? If the answer is yes, and you're 18 to 65, you may participate in an outpatient research study of an investigational medication for opiate addiction. If you qualify, you receive study-related care at Johns Hopkins Bayview Medical Center at no cost. Up to $1,950 is available in compensation.
George Bigelow, Ph.D., directs this study. Call 410-550-0007 for a phone interview.

Bipolar Disorder

Have you been diagnosed with bipolar disorder? Do you feel that medications haven't helped your mood symptoms? Do you sometimes have trouble concentrating? If so, **you may qualify for a 16- to 18-week study for treatment of bipolar disorder**, led by Jennifer Payne, M.D. We are looking for adults age 18 to 65 who are currently in treatment with an outpatient psychiatrist. Volunteers will receive study medication and laboratory tests and will be compensated.
E-mail: moodtrials@jhmi.edu or call 410-502-2586.

Bulimia Nervosa

Physicians with the Johns Hopkins Eating Disorders Program are seeking **women 18 to 35 years old with bulimia, to participate in NIH-sponsored research**. The study includes 10 weeks of outpatient treatment, a health assessment, blood testing and having brain images taken using a medical scanner. Participation is paid.
Angela S. Guarda, M.D., is the principal investigator. Call 410-955-3863.

Major Depression

This clinical trial aims to evaluate the effectiveness and safety of a new, once-daily, oral medication for depression called agomelatine. Participants age 18 to 70 diagnosed with major depressive disorder may be eligible. The study lasts up to eight weeks and involves at least nine visits to our clinic for study-related examinations and assessment. Those completing the study may also continue on the medication in a 52-week open-label extension phase.
Frank Mondimore, M.D., heads the research. Call 410-502-2586.

Parkinson's Disease Depression

If you feel sad and/or withdrawn, have appetite and/or sleep changes and lack concentration or motivation, you may qualify for this study. Investigators at The Johns Hopkins Hospital seek volunteers with Parkinson's disease, over 30 years old, for participation in NIH-funded research. The study offers free evaluation and study medication.
Laura Marsh, M.D., is the principal investigator at Hopkins.
Call 410-614-1242.

Parkinson's Disease Cognitive Problems

Johns Hopkins researchers are seeking volunteers with Parkinson's disease and memory problems to participate in a study funded by Forest Pharmaceuticals. Participants must be older than 50.
Laura Marsh, M.D., is the principal investigator at Hopkins.
Call 410-614-1242. ■

A Breath of (Mostly) Fresh Air

The search for a biomarker prompts a fascinating thought: Do bipolar patients have a learning disorder?

Ten years ago, psychiatrist **Dean MacKinnon** crawled into a spelunker's equivalent of a spider hole and it wasn't a jolly experience. On a caving expedition, he'd imagined walking through caverns, seeing stalactites. But after resting in a small, tight space, he says, "I suddenly felt rather desperate to get out." He couldn't seem to get his breath, and confessed it, sheepishly, to the guide. "Oh, that always happens here," was the reply. "It's the least ventilated part of the cave."

Now MacKinnon's understanding of what it's like breathing elevated CO_2 and his sharpened sense of the human urge for a good breath may have paid off. "I think it planted a seed," he says, one that, with diligence, could grow into a biomarker for bipolar disorder (BD). Because, by definition, biomarkers signal a disease cleanly—without the confounding effects, say, of violence in patients' lives or the expertise of their diagnosing psychiatrists—they're much in demand. So MacKinnon's intent on his search.

And the basis for such a marker? It doesn't hinge on a jump in cortisol or some other stress-related chemical, he explains, nor is it finding a nerve transmitter gone askew. Rather, it rests on the idea that at least part of BD comes from a disorder in emotional learning.

"The brain is primarily a learning machine," MacKinnon says. "It takes in sensory information, then puts two and two together for behavior that avoids danger and satisfies appetites."

And it's that so-called appetitive behavior that's the focus here. Classic bipolar disorder, of course, brings recurring highs and bouts of depression. But manic and depressed patients *also* find themselves either hypersensitive or numbed to appetite's influence on behavior: "Depressed patients have little motivation," says MacKinnon. "They've little zest for activities that normally bring reward—sleep, nutrition or socializing, for example." Conversely, someone in a manic state seems *driven* by intense and varied urges, to the point of being unable to manage them. All, he says, may stem from failure or inefficiency in conditioning, the most basic sort of learning.

Perhaps the chemistry within the brain's synaptic classrooms is altered—it may be no coincidence that some candidate genes for BD retool synapses. Whatever the biochemical flaw, the changes in patients, he believes, are what you'd expect with an inability to link need, behavior and reward. "My argument," says MacKinnon, "is that at times of stress or change, people with bipolar disorder can't maintain that sort of learning."

That's where breathing comes in. MacKinnon suspects that bipolar patients' possible difficulty in adapting breathing—an innate appetite-driven behavior—mirrors their inability to learn and regulate emotional behavior. His "aha moment" then, is using one as a marker for the other.

Recently, he ran a pilot study, asking patients to breathe air with not-harmful, slightly raised CO_2 for 15 minutes. People without BD respond by panting a bit to try to clear the gas. Then, after a few more minutes on the enriched air, breathing levels off to save energy as the body learns that only so much CO_2 can be removed.

In BD, however, breathing doesn't stabilize. The response in many is unpredictable, going up and down, Mac-Kinnon says, "like a faulty cruise control." Now he hopes a larger study will verify response to CO_2 as a biomarker. Plus, a new ability to study how appetitive drive is regulated could reach to the heart of major depression, dementia, cognitive disorders and eating problems like anorexia.

MacKinnon notes that lithium, a mainstay of BD treatment, is known to enhance growth of neurons—a help with learning. "But people need more than medication to get better," says MacKinnon. "I see this in my practice. Because patients with unstable moods don't know if they'll feel the same today about something as they did last week, their learning is imposed on chaos. They need encouragement, structure. They likely need repeated lessons, repeated episodes of doing something good and getting a reward." ■

Assistant Laura Lorenz breathes easily as Dean MacKinnon assumes his role as observer.

Cosmic Care

There's a move afoot lately to uncover underpinnings, to explore what keeps things going. Consider dark matter. The cosmic material has kept a low profile, but we now know it makes up some 90 percent of the universe.

On a quieter scale, it's not an artifice to see what **Gretchen Withrow** and her colleagues do in that light.

"Psychiatry values its social workers greatly—it's always done so—while it demands a high standard of care," says Withrow, who directs Hopkins Psychiatry Social Work. It's because of that, she says, that the staff of 17 is woven tightly into the fabric of the department. "Every psychiatry patient is routinely seen by a social worker," says Withrow, and doctors seek out their insights daily.

Mental illness, however, makes unusual demands. Because patients are so very environment-sensitive, for example, Withrow's staff works overtime to ease stress. They wrestle insurance plans "with near-abysmal mental health benefits" and form part of Psychiatry's pushback to the pressure to discharge patients prematurely.

Social workers conduct individual and group therapy. But the staple of their work, Withrow says, is holding family meetings. Such sessions open a window on a patient's illness in a social context—that's critical to plan treatment before and after discharge. And they also demand finesse. "Just as patients need outside help most, their illness can alienate a family or friends." Then Withrow's staff finds themselves holding a thread of a support system. Still, they persist, finding alternate housing or programs. What emerges more often than not is follow-up care with a chance.

"I'm proud of how we're able to help our very complicated patients," she adds. "It takes a skill set that's extraordinary." ■

Gretchen Withrow's no stranger to challenge.

BrainWise

This issue of *BrainWise* is published by Johns Hopkins Medicine Marketing and Communications for the Department of Psychiatry and Behavioral Sciences.

It is distributed to the scientific community, sponsors, friends and others interested in the department's research and activities.

Some of the research in this newsletter has corporate ties. For full disclosure information, call the Office of Policy Coordination at 410-223-1608.

To make a gift to the Department of Psychiatry and Behavioral Sciences, contact Jessica Lunken, Director of Development Department of Psychiatry 100 North Charles Street, Suite 410 Baltimore, MD 21201 410-516-6251

If you no longer wish to receive this newsletter, please e-mail mcentofanti@jhmi.edu

Editorial Office
901 South Bond Street, Suite 550
Baltimore, MD 21231

JOHNS HOPKINS MEDICINE

Non-Profit Org.
U.S. Postage
PAID
Permit No. 1608
Baltimore, MD