

## Schizophrenia: A sea change?

When **Akira Sawa** visited his native Japan this summer—he'd had an established psychiatric practice there—he was asked by friends to see their son, diagnosed with schizophrenia as a teenager. Over the years, the now middle-aged patient\* hadn't really responded to any medication. Deeply psychotic and depressed, the man had twice swallowed handfuls of aspirin but escaped serious injury.

The meeting had a profound effect on Sawa.

"I realized after the visit," he says, "how much that one patient reflected what we need to do for schizophrenia in the world in general and at Hopkins in particular." Now, in part because of fine-tuning taking place in Psychiatry's approach to schizophrenia (SZ), and partly due to dramatic opportunities for research partnerships (see box), Sawa, who heads Hopkins' Schizophrenia Center, envisions something of a sea change.

The goal is to improve life for SZ patients, and the Hopkins route there will likely become more global, including more clinical research with a sharpened focus that builds on the department's already strong patient care and bench science.

Look again at the Japanese patient. He resisted taking his pills. "And he had never been prescribed clozapine," says Sawa, "though it's probably the most effective compound for treatment-resistant schizophrenia." Clozapine was approved a mere two years ago in Japan due to concerns about side effects, and use there still is uncommon. Those concerns, while serious, were addressed years ago in U.S. centers, through targeted prescribing and closer patient monitoring.



Psychiatrist Crystal Watkins (left) and researcher Hanna Jaaro-Peled (right) reflect Akira Sawa's push for an even closer working of the two disciplines to hasten new therapies for schizophrenia.

"So global health means we might offer useful approaches not realized in other countries," Sawa says. He envisions monitoring internal health systems worldwide: "If we learn what's missing in, say, China, the Middle East or Africa, we can suggest partnerships for education and care. Far from being one-sided, the collaborations would benefit everyone." For example, he adds, if they resulted in worldwide clinical trials, the larger numbers would make results more trustworthy and hasten therapy.

Meanwhile, at Hopkins, the clinical research infrastructure and expertise needed for good trials have long existed in the Meyer 5 unit under clinician-neuroscientist **Russell Margolis** (page 2). And Sawa draws on his own deep experience in SZ's basic science research, as well as clinical

skills, to suggest two new hypotheses to test—low hanging fruit that could yield benefits more quickly.

The first idea is that early intervention can make a difference in treating schizophrenia. Underlying that are just-finished studies at Hopkins and elsewhere showing major changes in brain neurochemistry and anatomy shortly after SZ's onset. Yet current treatment, Sawa points out, aims most at *chronic* illness. The real need is to detect the disease early—*think biomarkers*—and find who's most at risk.

The second hypothesis, that SZ is systemic and not confined to the brain, stems from news that certain antipsychosis medications raise patients' risk of obesity and type 2 diabetes—the troubling metabolic syndrome. "But what if schizophrenia

### Building on success

Opportunities have opened at Hopkins to improve schizophrenia's outlook in ways that go beyond research. There is also support for medical training and public outreach:

- Hopkins' respected **Brain Science Institute** has targeted schizophrenia as its psychiatric illness of choice for multidisciplinary research—from the molecular biology onward.
- The multimillion dollar **Lieber Institute for Brain Development**, dedicated to revealing SZ's early biology, just opened adjacent to Hopkins' campus. Lieber's work to catalogue patients' tissues, genomes and gene activity offers, as one Hopkins collaborator says, "a most wonderful encyclopedia for scientists."
- A designated **Conte Center** since 2008, Hopkins Psychiatry continues to funnel NIH funding into high-quality translational and clinical SZ research. Grantee Akira Sawa sees a new synergy coming from collaborating brain imaging scientists, epidemiologists, geneticists, molecular neuroscientists and clinicians.

*itself* does something to the body that makes people more prone to this?" Sawa asks. "Understanding the underlying process might not only let us damp down metabolic syndrome and end that side effect, it might also make patients more open to taking medication."

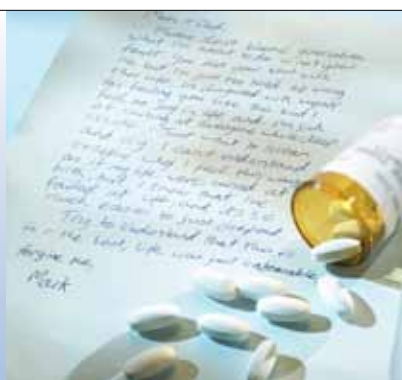
It's possible, he speculates, that—like the tail wagging the dog—addressing the syndrome might work on some of schizophrenia's harder-to-treat symptoms. "All this is open to explore," says Sawa. "The time is ripe and we're in an ideal place to find answers." ■

\* Some details were changed to protect patient privacy.

### Genetics and attempted suicide

The link grows stronger.

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Older studies may be wrong.

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New work points to a culprit circuit.

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We believe the superb clinical care we provide every day to our patients—whether near us in Baltimore or referred from around the world—stands as an essential part of our tripartite mission of clinical care, research and training.

*I should like to see a clinic give one half of its beds to intensive work on special clinical programs.* With these words, our founder Adolph Meyer launched the Phipps Clinic at Hopkins a century ago. What began as Meyer's directive to care for the whole person—he termed it *psychobiology*—evolved into a focus on each patient's disease, temperament, behavior and unique life story: the four “perspectives” that frame our patient care and guide our teaching today. It is the Hopkins way.

Yet what also shines through is our passion for the research that improves the treatment we give patients. We invite you to learn more about us from this issue of *Hopkins BrainWise*, and to contact us if we can be of help.

J. Raymond DePaulo  
Chairman Director, Department  
of Psychiatry and Behavioral  
Sciences

## A natural brake for Huntington's?

*A therapy could lie in mending nature's feedback loop.*

With Huntington's disease, psychiatrists set their jaws and their shoulders—figuratively, at least—and offer patients what they can: relief of some symptoms, the best palliative care possible and a large helping of concern.

The fatal genetic disorder, from a single, dominant gene mutation, remains incurable. And though the flaw in the HTT gene was made plain almost two decades ago, there's nothing yet to slow the disease's progressive dementia, let alone stop it.

But this summer, a Hopkins team led by psychiatrist **Russell Margolis** reported studies that are rare in that they raise possibilities. Margolis' group has uncovered a natural feedback loop in the body that might be “gamed” from the outside to shut off or damp down the mutant gene and block its harm.

“The principle is there,” says Margolis, “even though it's early days by anyone's measure on a path to therapy.” Early or not, the find is important and not just because it's a glimmer in an otherwise dark disease.

A variety of strategies exist to stop gene-based degenerative diseases in the brain, some farther along than others. Huntington's researchers have been exploring siRNA, for example, engineering bits of nucleic acid that—like masking tape—appear able to silence the mutant HTT gene in cell cultures and test mice. “It's not without hurdles, though,” Margolis says. “Safely getting siRNA to exact targets in patients' brains may prove difficult. A more natural way may exist, though, to knock down the Huntington's gene.” It involves the brain's molecular ability to regulate itself.



“Feedback loops could be at work in many diseases,” says Russ Margolis. “Will we try to exploit that for treatment? Yes!”

Some of what's amiss in Huntington's, it seems, stems from loop trouble.

When HTT is mutated in disease, the team found, the nearby antisense gene becomes far less active. Lacking the brake, mutant HTT goes unchecked and freely codes for its toxic protein product.

In a satisfying proof of principle, however, Margolis' group found they could reverse the glitch. After artificially raising antisense activity in cells—*fixing the brakes*, in effect—the team could find no trace of toxic Huntington's protein.

Is there therapy in this? The thought is tantalizing. “If you find a drug that tells cells to make more antisense, wouldn't that, in theory, knock down the Huntington's gene?” Margolis has already picked collaborators to help find out. ■

That idea has unfolded over the last two years, Margolis explains, beginning with his team's analysis of target DNA in healthy mice and humans. Work that focused first on the single strand carrying the Huntington's gene, then on its opposing DNA strand uncovered a new gene. Sophisticated follow-up studies showed the opposing gene to be widespread in the brain and able to be turned on.

Most important was the find that the new “antisense” gene, as it's called, can inhibit HTT. “It acts as a natural brake,” Margolis says, “and that's likely why it's there. It's part of one of those feedback loops so common in biological systems.”

### CLINICIAN UPDATE

## The genetics of attempted suicide

The idea that genes play a part in the chance that a person with bipolar disorder will attempt suicide—as opposed to just thinking about it—isn't new. Large epidemiological surveys and twin studies, for example, suggest that.

But a recent study of the DNA of some 2,700 adults with BP, carried out by mostly Hopkins psychiatrists, went further than usual: The study results tied four genes on a narrow region on chromosome 2 to increased risk of ending one's life.

One gene called ACP1 especially stood out. The researchers found more-than-normal levels of that gene's enzyme product in brain tissue

of the disease's suicide victims. Interestingly, the enzyme can affect the same biological pathway as lithium, a therapy prescribed, in part, for its antisuicide properties.

The association of gene and behavior in patients with BP was clear: Those carrying one copy of an ACP1 variant were 1.4 times more likely to have attempted suicide. And those with two copies of the less typical ACP1 were almost three times as likely.

“What's promising are the implications of this work for learning more about the biology of suicide as well as the medica-



tions to treat patients who may be a risk,” says researcher Virginia Willour. “Not everyone with bipolar disorder can take lithium because of its side effects,” she adds. “If we could give people another option, that would be fantastic.”

The team was able to repeat their findings in another study group, one with DNA samples from more than 3,000 people with the disease.

Work of this sort is crucial: Of those with bipolar disorder, 47 percent think of killing themselves, while 25 percent actually try to do it. That's a far cry from the entire U.S. population, where 4.6 percent make attempts. ■

# Our variety's showing: A sampler of new work



## Straight story on cutting

*Sometimes people do things to hurt themselves on purpose, like cutting, scratching, burning or injuring themselves in other ways. Have*

*you ever done something like that?* It's not a typical college questionnaire question, but psychiatric epidemiologist **Holly Wilcox** wanted better information on non-suicidal self-injury (NSSI) that mostly targets adolescents. Small studies have offered likely risk factors and motives, but a larger study that follows people over time could help predict and prevent the troubling behavior.

Wilcox's team interviewed more than 1,200 college freshmen, checking on them annually through college and assessing, for example, NSSI frequency, the students' ability to regulate emotion and their breadth of social support.

Among the findings: NSSI in this age group often repeats itself. And having depression, a depressed mother, homosexual orientation and poor ways of controlling emotion especially point to future bouts of self-made injury.

For information: 410-502-0629.

## Olanzapine? Can't say no to dough

When olanzapine (OLZ) appeared in the 1990s, clinicians were heartened at having something new for psychosis. That turned to dismay as the useful agent's possible metabolic side effects—obesity and diabetes—became clear. To help explain OLZ's dark side, **Kellie Tamashiro** and colleagues studied rat models' response to the drug, both short and longer-term. Control animals were offered plain sugar cookie dough for either five days or three weeks. Test counterparts got dough dosed with OLZ.

By study's end, rats on olanzapine were roughly 10 percent heavier, thanks, the team found, to a fairly dramatic appetite increase

early on. They stayed fatter throughout—the gain was due to fat—though appetites later dropped. And they'd become less insulin-responsive. A profile of regulatory neuropeptides in the animals' brains revealed a pattern that's typical of calorie-starved people who are moved to eat.

For information: 410-614-9151.

## Stress's environmental toehold?

Serotonin-based pathways in the nervous system rule, in part, over the body's response to stress. So it's no surprise that the serotonin transporter—the molecule that ferries "spent" serotonin out of synapses—has been under scrutiny. The thought is that flawed serotonin transport somehow upsets a person's ability to adapt to stress.

Study of the transporter extends to its gene. Apparently, a number of downsides come with having a shorter version of that gene's regulatory part, including subtle brain abnormalities and a tendency to depression.

To verify the stress/gene interaction, a team including **Dimitrios Avramopoulos** studied 1,875 new recruits into military service, a banner time for stress. Recruits carrying pairs of genes for the transporter's short form, the team found, were indeed more likely to show paranoid or defensive reactions under boot camp's rigors.

For information: 410-955-8725.

## Master molecule rules fat and more

Neuropeptide Y, well known for increasing



appetite, is surprisingly more of a jack-of-all-trades, according to a recent lab rat study. The work, led by **Sheng Bi**, in which expression of the protein in the brain's

hypothalamus was damped down, suggests NPY is critical in regulating body weight: It affects how much is eaten, what kind of fat results, levels of body heat and energy expenditure. That's not to mention urges for physical activity.

Most interesting is that lowering hypothalamic NPY in the animals turned off the overeating that high-fat diets prompt and the obesity that follows. It enhanced sensitivity to insulin. To the researchers' near-amazement, it also shifted the animals' white fat into energy-burning brown fat. It's a treasure chest of targets, they say, for obesity and diabetes.

For information: 410-502-4789.

## More enzyme, less nice to be near

Antisocial personality (ASP) traits like irresponsibility, lack of remorse or deceitfulness are all too common. And because people with more than one trait typically push hard on society's boundaries, there's interest in finding what mix of genes and environment brings traits out. Studies in the 1960s raised the intriguing idea that those with ASP are short on monoamine oxidase (MAO)—the enzyme that clears serotonin, norepinephrine and dopamine from synapses. Mice with low MAO, for example, are Feisty with a capital F.

Newer work found that people vary in the regulatory part of the MAO gene that oversees how much enzyme is created. It's reasonable to think, then, that those with a low-producing gene are more prone to have the antisocial traits.

The trouble is that human studies aiming to show that have muddy results. **Irving Reti** suspects the reason isn't so much biology as it is environment: The effect of a bad childhood likely swamps the data.

So Reti's team divided a large number of participants in a Baltimore community survey—narrowed to people with ASP traits—into those with childhood abuse and those without. That made the association between antisocial behavior and available MAO stand out clearly.

For information: 410-614-1732.

## More drama from the trauma

A mugging. A terrible burn. The ability of severe trauma to set off acute stress disorder within days, or PTSD some weeks later, is well known. But how to predict who'll go on to suffer them after a traumatic event and who won't? Finding a biologic marker for people whose hypervigilance and other characteristic symptoms will be longer-lasting is a firm step on the road to tailored therapy. Looking solely at burn patients, **Neda Gould, James Fauerbach** and their team focused on heart rate and blood pressure. The latter wasn't a predictor. But high heart rate in the ambulance after a burn occurs, they found, foreshadows a higher risk of acute stress disorder or PTSD some six months after a patient leaves the hospital.

For information: 410-550-0890.

## When mother hovers

We all know mothers who insert themselves into a child's life, and though their intentions are good, that doesn't seem right. Solid study agrees: Maternal over-



control is clearly linked with higher anxiety in children. But how? **Golda Ginsburg** says it has to do with undermining a child's sense of competence. Now

her new work supports that. In a study of 89 mother/teen pairs, the outcomes show that having mothers who need to know a child's every move, for example, results in offspring who feel less than capable as well as more anxious. The idea, Ginsburg says, is that parental overcontrol teaches children they're not able to handle many situations and that, in turn, leads to high anxiety.

For information: 410-955-1544.

## THE BENCH. THE BEDSIDE.

A constant wash of the stress hormone cortisol increases body fat and risk of the evil trinity: diabetes, coronary artery disease and osteoporosis. That's not to mention rearranging synapses, disturbing cognition and mood and lessening brain mass—all while thwarting nerve cell regrowth.

**Being able to measure a patient's cortisol "burden" over time, then, is highly desirable—proof, for example, that life changes are in order.** But a way to measure average cortisol levels over time is elusive because they fluctuate so, even within a single day. So **Gary Wand's** team has hit on an indirect tactic. It's based on the stress response gene, Fkpb5. The gene—which has a role in stress-

sensitive psychiatric disease like PTSD—changes structurally during long-term cortisol exposure.

The team found that in mice with month-long artificially elevated cortisol, Fkpb5 showed matching epigenetic changes. The next step is to see if the changes hold in more realistic social stress situations.

Call 410-614-0056.

**Brain opioids take center stage in regulating feelings of pain and pleasure. They also influence alcohol's effects and the desire to drink. But how?** In new PET studies run by **Betsy McCaul's** team, people dependent on alcohol were compared with social drinkers. The former clearly had a denser outlay

of key opioid receptors in brain areas tied to alcohol reward, dependence and craving. What caused the receptor uptick? Was it alcohol withdrawal? Long-term excessive drinking/dependence? A person's native genes? Childhood adversity or chronic stress? More research will tell, says McCaul.

Call 410-955-9526.

Naltrexone cleanly blocks the effects of heroin and other opioids. And unlike the methadone or buprenorphine used as addiction therapy, you can't overdose on it; it gives no "high." **Naltrexone would be ideal in addictions clinics if only patients would take it.** **Kenneth Silverman's** team,

**however, sees an opening, an option that could increase willingness.** In a study of 38 detoxified dependent adults, the team offered the added option of training in a workplace situation and being paid in redeemable vouchers. One group had to take (new extended-release) naltrexone in order to work. The other half could earn vouchers, but getting naltrexone was optional. Result? Those compelled to take naltrexone in order to work stayed with the therapy far longer.

Call 410-550-2694.

**Binge eating not only changes brain chemistry, but bouts of overeating fats and sugars may change it in a way that,**

**ironically, encourages the problem. To clarify what's going on, Angela Guarda** has studied the distribution of cannabinoid receptors—yes, like that cannabis, though the cannabinoids involved here are self-generated—in brain areas tied to food intake and body weight. Her team worked with rats offered sweetened Crisco under various conditions that reflect aspects of human binge eating or dieting habits in patients with eating disorders. The rat brains showed characteristic decreases in the density of these receptors in key brain regions, depending on the lardy treat's availability.

Call 410-955-3863.

# A slower road through dementia

*Alzheimer's progression isn't always as fast as we thought.*

**P**aging through test results of people with Alzheimer's disease—those in long-running studies out West that he's helped direct for years—often puzzled **Kostas Lyketsos**.

What his discerning eyes and ears told him—he heads Hopkins' Memory and Alzheimer's Treatment Center—was that, yes, the men and women were growing worse, but not at the pace that earlier studies worldwide predicted.

So Lyketsos was eager for the bottom line on a recent study-within-a-study that he and colleagues ran to quantify the disease's progress in 328 elders in Cache County, Utah, with possible/probable Alzheimer's. For roughly four years, beginning with dementia's onset, participants were rated on cognition and ability to function. Researchers also checked common neuropsychiatric symptoms like depression, apathy and agitation using a classic inventory.

Results showed that dementia progresses slowly in a surprisingly significant number of patients—more than a quarter of them. “In that group,” Lyketsos says, “thinking ability and life skills change very little for some three or four years after dementia begins.”

And the faster course others describe? That reflects a skewed sample, he explains, “a classic selection bias” in measuring patients who refer themselves to clinics, rather than those in the general population. Clinic patients tend to be younger and more likely to have a spouse who encourages them to seek help earlier for their more aggressive disease.

“There haven't been many *population-based* studies,” says Lyketsos, “and they're important for us to get the complete picture.”

When it began more than a decade ago, the “granddaddy” project—the Cache County Study on Memory in Aging that's long involved Hopkins researchers—enrolled some 5,000 county residents, most of them seniors. The Utah site was singled out nationally because of uniformity: Folks there have fewer chronic illnesses and most of the population lives at home. Also, life expectancy is longer.

This newest study could yield solid benefits in



“Alzheimer's studies in the 1980s suggested a much faster disease for everybody,” says Kostas Lyketsos. “Now we know that's not true.”

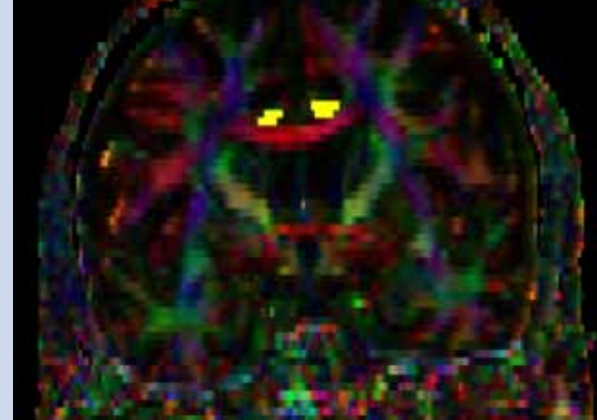
expanding the drug pipeline. Previous trials of potential Alzheimer's medicines, for example, measured benefits using a clinic-based yardstick. Yet, Lyketsos says, “it's possible some drugs given a thumbs-down in clinic-based studies would actually help many patients with less aggressive disease.

“Also, we need to ask what's special about these slow progressors. Could they tell us how to slow the disease significantly for everybody?”

Another find surfaced from the new study—this one from focusing on the neuropsychiatric symptoms. “Over time, every patient gets them,” Lyketsos says, “but looking at any one person's course, we see that, unlike cognitive symptoms, these typically fluctuate a lot.” A patient's aggression, for example, can ebb and flow.

“If these symptoms, the most disabling, can improve on their own, even temporarily,” he asks, “we could hope there's some way to keep them from returning.” ■

*For information: 410-550-6337.*



Diffusion tensor imaging highlights a brain circuit suspect in Alzheimer's common irritability.

## A brain path for grumpiness

Irritability. Agitation. The two neuropsychiatric symptoms are common in both the mild cognitive impairment (MCI) that can shade into Alzheimer's disease (AD) and in the disease itself. Of course, even healthy people are occasionally visited by irritability or agitation that arise like so many gnats in the psyche, but their frequency in major brain disease—as well as the anguish they prompt—demands research.

Now a new imaging study ties a probable brain area to those symptoms. It also strengthens the idea of flawed brain conductivity as a source of psychiatric disease.

Recently, **Sarah Tighe**, a postdoctoral fellow under mentor **Gwenn Smith**, and colleague **Michelle Mielke**, explored brains of 45 older patients—about half of them with MCI and half with mild AD—using diffusion tensor imaging (DTI). The technique highlights the white matter tracts that connect brain areas.

Tighe focused on the cingulum, a nerve fiber bundle leading to the frontal brain, specifically to the anterior cingulate cortex that's linked to depression and bipolar disorder as well as AD.

In imaging the cingulum, however, Tighe's study probed the path rather than the destination. “We suspect difficulties in the circuit,” she says. “Lately we've seen a paradigm shift within psychiatry—one that says focusing on a single brain area as a source of illness is too simplified. Now we're thinking more about conduction between the bits.”

Fortunately, DTI can pick up flaws in nerve fiber orientation—like finding a missing or misplaced stick in a bundle. A drop in this property is a flag for ailing white matter tracts.

In the study, clinicians evaluated patients for neuropsychiatric symptoms such as apathy and low mood as well as irritability and agitation before they went under the scanner.

“What we found,” says Tighe, “was that irritability and agitation were best explained as having compromised white matter in the anterior cingulum. That makes the structure—and its circuit—suspect.” The cingulum involvement also suggests a common biology for agitation and irritability in late-life depression. ■

*For information: 410-550-2204*

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