



## When Depression Is Elevating

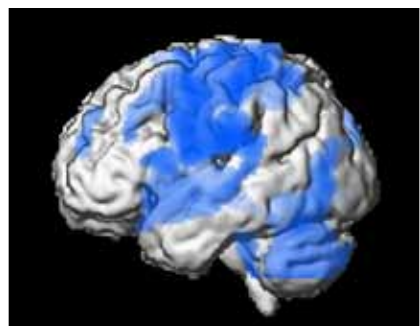
Research has laid to rest the myth that what looks like depression in older people is just a response to what life throws at them. It's the myth that stiff joints, fading hormones and a surfeit of funerals can get people down, but they don't have an actual mood disorder.

The idea persists, however. And benign it's not.

Trustworthy sources estimate that roughly a quarter of Americans age 65 or older experience either frank depression or the one-step-down of chronic dysthymia or the still milder "subsyndromal" mood disorder that skulks below clinicians' radar screens. With its higher rate of relapse and of suicide, late-life depression is a major public health problem.

For all that, the pathology of "melancholia" is poorly understood in this particular age group. That's in part because there's a second myth to cross off: that biologically, depression is depression, no matter what the age.

But a growing body of work by



Overlap? Compare the PET-scanned high metabolism of old-age depression (red) with the metabolically grim areas of mild Alzheimer's (blue).

neuropsychologist **Gwenn Smith**, with Hopkins colleagues and others, shows subtle but telling differences in what elders suffer. Their affected brain circuitry is different, for one thing, she says, as is its metabolism.

Smith's studies not only suggest a way to tell, at that age, who won't respond well to antidepressants, but they also hold a hope of understanding depression's impact on the brain. What drives Smith these days—the proverbial carrot—is a tie-in to Alzheimer's disease (AD). There's the teaser that the seeds of late-life dementia are planted in the very brain abnormalities she's found in depression.

"I didn't start as a mood disorders researcher," Smith explains. "My interests were originally in AD and in aging." As an undergrad, she had worked in the first lab to use radiolabeled glucose to map human brain metabolism. Then she grew skilled in those PET scanning methods and others as a postdoc, applying them to patients with dementia.

One reason that assaying metabolic changes throughout the brain is hugely useful is because it can spot areas of change in nerve function, often before pathology has settled in. In Smith's early AD work, for example, key association areas of the cortex stood out. And the lights were turned off, metabolically, in those tissues.

Her shift to study late-life depression came in part after epidemiological reports—a key one was from Hopkins—suggested that having it raises the risk of Alzheimer's. "Of course, our first question was *how?*" So Smith recruited older, depressed people for study, "expecting full well that their metabolism would hit a middle ground between healthy seniors and AD patients."

But Smith was surprised: Rather than being down a tad, brain metabolism is elevated in cortical areas in



Gwenn Smith explores the intersection of depression and Alzheimer's disease. "It's amazing," she says, "how it seems to fit together."

late-life depression. Why that's the case isn't clear. The metabolic overdrive, she suggests, could mean the brain's trying to compensate for the onset of pathology. "We now believe that late-life behavioral symptoms like depression or unusual irritability may reflect something wrong in the brain."

It gets more interesting. The "hyper" areas, which include parts of the superior and middle frontal cortex, some temporal and parietal regions, lie in a "default network"—tissue that normally maintains a hum even when the brain is at rest. There's more: After hearing Smith lecture, a friend pointed out that the overactive areas overlap Alzheimer's

metabolic dead zones. "Could it be," Smith asks, "that these areas just burn out?"

Also intriguing is that in several PET studies, Smith has shown that antidepressants return metabolism to normal in many older patients. And significantly, how much it drops after one dose predicts if depression will lift with longer treatment.

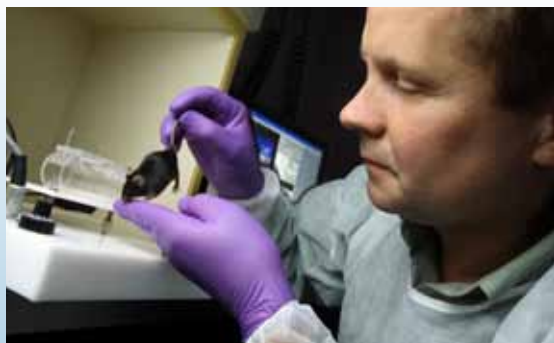
Now she's entering a key phase of her work: finding what underlies the metabolic shift and what that says, if anything, about dementia. The dots are there; Smith just has to connect them. ■

For information: 410-550-0062.

### Magic Model

New mouse tackles nature vs. nurture in schizophrenia's cause.

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### A Panic Personality?

View this and other highlights of new Hopkins research.

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### On the Brink of Going National

Drive and research carry a teen depression program forward.

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## Doing Our (Unilateral) Bit for Therapy

This issue of *BrainWise* is a simple act of consciousness-raising. As new molecular and brain-imaging tools edge us close to breakthroughs in severe mental disorders, that and a clear need for a new generation of therapies have sharpened our scientists' drive. The quality of our research is at a high point, as we show here.

But we can only advance so far on our own. The public should expect us, no, demand of us, that we also collaborate with pharmaceutical companies. In the best of all worlds, drug companies want to develop specific, effective, low-cost treatments with few side effects. And so do we.

These past two years, however, questionable and conflicted relationships have undermined professional partnerships with Pharma. Apparent conflicts of interest by clinician-scientists and institutions—not Hopkins—have aroused both congressional leaders and the public.

These conflicts undermine academic researchers, most of whom work hard and play by the rules. Why is this happening now? I think a change in economic rewards and incentives has reshaped behavior.

Thirty years ago when I was junior faculty, some

companies would hire only sales reps who were registered pharmacists or had advanced science degrees. Since then, it's become clear to Pharma that a dollar spent on R&D can't match the return of a dollar spent on marketing. Industry doesn't depend on us to advance their research now so much as to act as "opinion leaders" to advance sales. To my mind, this has whittled away most of the good that we can accomplish together.

Correcting this is far from simple and likely calls for a radical review of FDA policy and perhaps patent laws. My pipedream is that drugs which are not truly novel should get a short patent life, while truly novel medications would get much longer patent protection—it's a tactic to encourage new drugs based on new mechanisms.

R&D carries high risk, no doubt about it, so we must provide incentives for Pharma and medical researchers to ride this wave of scientific breakthroughs together. Our patients need better treatments! ■

J. Raymond DePaulo, Jr.,  
Henry Phipps Professor and  
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## Where the Twain Could Meet

*New model mouse has potential to tell how the environment shapes schizophrenia.*

It's enough to make you hold your breath these last few years, watching the certainty creep into our ideas on what makes schizophrenia. That the disease runs in families is sure. But environment's role in it has always been a smoking gun: Prenatal exposures to flu, for example, or teenage marijuana use or being born in winter all heighten risk. Just how, though, is elusive.

Lately, convictions about a gene/environment connection in schizophrenia have tightened, with studies by Hopkins' **Mikhail Pletnikov**, M.D., Ph.D., and others playing their part. He began by examining varying genetic strains of rats exposed to a common environmental virus as newborns. Some developed what's for all intents and purposes rodent schizophrenia. Others were just fine.

Pletnikov took the work further to show that viral infection in the more vulnerable rats touches the same monoamine brain systems as the human disease.

"But as much as the studies with different strains say, *yes, genes and environment probably work together to produce schizophrenia*," he explains, "it doesn't take us far enough. You don't know *which* genes are important or how environment steps in." It's also difficult to get a handle on the importance of timing. Does it matter if, say, Borna virus strikes a mother early in pregnancy's first trimester? Later on? Knowing that is a crucial clue to pathology. It would guide therapy for a disease that shadows the brain before birth but doesn't make itself known until young adulthood.

So recently, when Hopkins colleagues created schizophrenic mice based on a *single* faulty human gene, Pletnikov's team was quick to adopt the cleaner, simpler model. "We have well-founded hope," he says, "that we can get cell cultures and live animals to show how the environment brings changes to a vulnerable nervous system."

Pletnikov and **Christopher Ross** went on to refine the model, making one in which the suspect schizophre-

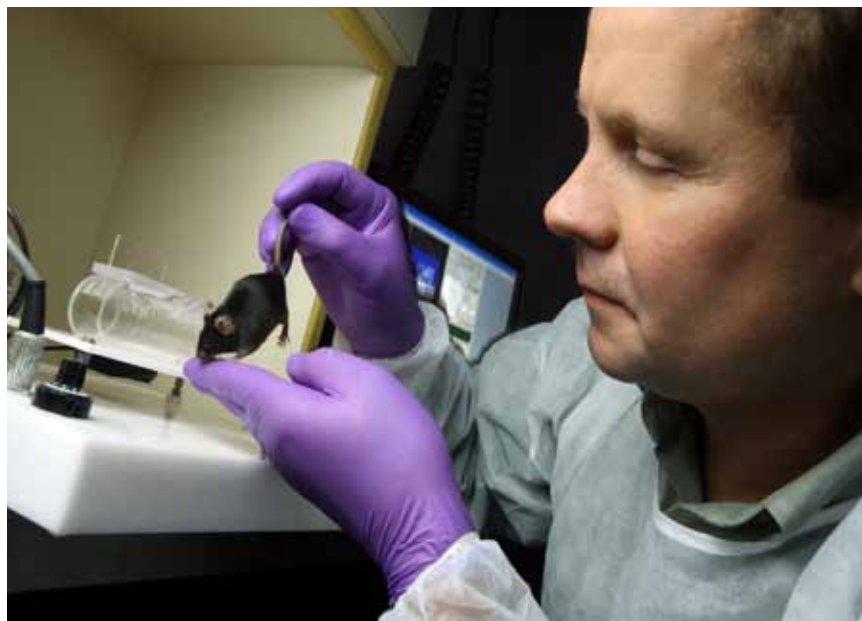
nia gene—called DISC1—is inducible. You can turn mutant DISC1 off by lacing a designer mouse's food or water with an antibiotic.

"Ultimately," says Pletnikov, "we hope that will tell us if sensitive periods exist in schizophrenia—times when a primed, developing brain can be derailed by environmental stressors." If the "prime time" is between birth and adolescence, the thinking goes, then perhaps blocking or heading off the stressor would also head off the disease.

"It's not very likely that *everything* is set in stone before birth," Pletnikov says. "But we don't know how plastic these things are in infant mice or humans. This model will help us figure that out."

The Hopkins scientists have been laying groundwork for timing research. They've measured baselines by comparing mutant DISC1 mice and healthy animals after both were exposed prenatally to a virus-mimicking agent. As expected, definite differences exist. Studies varying when DISC1 is expressed come next. "We have ambitious plans for this model," says Pletnikov. ■

*For information: 410-502-3760.*



Just how mice respond to an unexpected noise can reveal suspect wiring, says Pletnikov.

## Our Variety's Showing: A Sampler of New Work

### The More You Eat, the More You Want

Doughnuts. Peanut butter cups. Not only are they unhealthy foods, but eating them in a less-than-circumspect way may be a form of self-sabotage, a new study suggests. Work by **Nicholas Bello** and colleagues in Hopkins' Eating Disorders Program showed that either chronic overconsumption or binge eating of a mixture of Crisco and sugar causes a scaling-back of mu-opioid receptors in the hindbrains of standard lab rats. That's probably a response to the outpouring of natural opioids—molecules of encouragement. “The results are interesting,” Bello says, “because we see changes in a brain area that controls how much you eat at a meal.”

The idea is that overconsuming fatty sugarplums by rats or humans may prompt further binge-eating behavior. *For information: 410-955-2996.*

### A Panic Personality?

A tie exists, studies say, between panic disorder and the habit of coping with life by becoming overly dependent on other people or by avoiding certain things. But what sort of tie? Do the traits themselves predict or somehow encourage the psychiatric illness? Or is the opposite true, that early inklings of panic symptoms mold an avoidant/dependant personality?

To sort it out, psychiatrists **Joseph Bienvenu**, **Gerald Nestadt** and colleagues sifted data from a longstanding epidemiologic survey, finding adults who admitted excessive timidity, hypervigilance or the like but who had no overt mental illness. Then they checked follow-up data gathered some 13 years later.

Did the suspect traits predict—not necessarily cause—panic disorder and/or agoraphobia? “Yes,” says Bienvenu. “And knowing that is indispensable to understand these disorders in all their complexity.” *For information 410-614-9063.*



### Cocaine: When Abuse Turns to Addiction

Of the major illicit drugs, cocaine is most likely to lead takers from regular use to dependence. What “flips the switch” is an amalgam of genes, environment and developmental and social factors. Little's known, however, about the specifics.

A recent study by Hopkins' Behavioral Pharmacology Research Unit sheds some light. The researchers compared cocaine abusers to a matched group frankly

dependent on the drug. It's no surprise that the dependent group desired and valued cocaine more highly. Less expected, though, were the similarities: Both groups reported equal impulsivity. Most physiological and other responses to test doses of cocaine were also the same. The exception? Abusers reported more suspiciousness and showed more irritability and other unpleasant effects that cocaine brings.

Perhaps greater sensitivity marks those who don't slip into dependence. *For information: George Bigelow, 410-550-0035.*



### When Anxiety's Apple Falls Close to the Tree

Children of clinically anxious parents are up to seven times more likely to suffer anxiety illness themselves. Yet no adequate studies have tackled the problem with at-risk children.

Psychologist **Golda Ginsburg** designed the Childhood Anxiety Prevention Study to see if the cognitive behavioral techniques that help children with existing anxiety disorders might head off problems in healthy kids. Forty children age 7 to 12 and their parents participated in a program to increase resilience, instill hope and raise awareness of anxiety's known risk factors and how to whittle them. Half got the program immediately; the other half waited a year.

At year's end, 30 percent of untreated youngsters developed an anxiety disorder. None in the CAPS program did. It's no surprise their parents were delighted. *For information: 443-287-4349 or e-mail CAPS@jhmi.edu*

### Postpartum Gene Search Yields a Bright Spot

In one of the first studies to comb the human genome for genetic ties to mood disorders in new mothers, **Pamela Belmonte Mahon** and **Jennifer Payne** found a gene that's a prime target for future study. Turning to two large existing databases, their team analyzed DNA sequences of 1,000 blood samples—all from women in an NIMH study of bipolar disorder or one on those with recurring depression.

After an initial pass linked suspect DNA variations to chromosomes 1 and 9, the researchers fine-mapped the chromosomal areas of interest. One gene, **HMCN1**, stood out. That it's expressed in the brain and codes for estrogen receptor-binding sites makes it an attractive candidate. *For information: 410-502-2586.*

### Schizophrenia: Skin Gives You the Skinny

It's a schizophrenia researcher's fantasy: to create cultures of neurons from living patients—cells touched by flaws that underlie the disease. “You can't study function in cells in tissue from autopsies,” says **Russell Margolis**, who heads Hopkins' Schizophrenia Program. And grave concerns limit use of patient reproductive or embryonic tissues. So Margolis and colleague **Christopher Ross** have seized on the newly found ability to sample skin fibroblast cells from consenting patients—it's but a pinprick—and convert them into induced pluripotent stem (iPS) cells. Those in turn are transformed into true neurons.

A pilot study to derive neurons has begun. If they indeed model patient cells, they're one mighty tool to clarify schizophrenia pathology and test new drugs. *For information: 410-614-4262.*

### The Anxiety of Parkinson's

Clinical-level anxiety dogs too many Parkinson's disease (PD) patients. But documenting its nature and scope—a start to seeing that the most patients get the most help—hasn't happened.

To that end, geriatric psychiatrist **Gregory Pontone** and a Hopkins psychiatric team surveyed 127 PD patients in great depth. Almost half reported an anxiety disorder at some time in their lives, with 43 percent in the midst of one. Their most frequent diagnosis—the DSM's *anxiety disorder not otherwise specified*—includes PD-specific fears such as being unable to move in a public place or panic attacks when drugs' benefits wear off. Panic disorder, generalized anxiety disorder and phobias weren't uncommon. A surprise: The most anxious patients had intensified physical (motor) problems—something, Pontone says, that could help predict PD's impact. *For information: 410-614-0308.*

### GOSPEL Waylays the Downhill Path

Having complicated labor raises the risk of schizophrenia. A stroke or heart attack ups the immediate likelihood of depression. What these events hold in common is an unfortunate cut in the brain's oxygen supply, tripping a “stress cascade” in cells. Certain diseases with a psychiatric turn—like Parkinson's and Alzheimer's—also turn on oxidative stress pathways.

Recently **Akira Sawa** uncovered key steps in what comes next, showing that ultimately, oxidative stress can alter gene expression. The gene changes—they're epigenetic—at worst bring about cell death or, Sawa speculates, they hobble the brain in ways typical of psychiatric disease.

Most exciting is Sawa's discovery of GOSPEL, a natural protective molecule that interrupts this downhill path in lab animals, and the likelihood that a prescription drug, deprenyl, can mimic it. *For information: 410-955-4726.*



Patients on methadone therapy often struggle with other drug use and psychiatric disorders. **But routine treatment combining methadone with monthly counseling brings too-slow results for the most poorly responding patients.** A study led by **Karin Neufeld** rated Community Access Specialized Treatment, a network of Baltimore clinics with common access to short sessions of a new, “top drawer” program for patients who need more help. CAST, which includes on-site psychiatric care and tailored substance abuse services, proved much better on key outcomes measures than the single-clinic system. Call 410-550-0145.

Microglia, the nervous system's resident immune cells, release a brew of inflammatory molecules—cytokines—when they're active. Alzheimer's disease researchers know that the signature substance in AD-affected cells, amyloid- $\beta$ , potentially stimulates microglia. **Paul Rosenberg and Adam Kaplan hope to tap into all this to develop a marker for Alzheimer's disease.** By sampling key blood cells for cytokine levels, they've found that what AD patients release is in proportion to poorer cognitive performance. Call 410-550-9883.

**Two already FDA-approved drugs—one for epilepsy, the other an antidepressant—recently inspired optimism as they moved up the investigational pipeline for Huntington's disease.** **Christopher Ross** reports on studies with **Wenzhen Duan** in using a respected mouse model of Huntington's he'd developed earlier. Tiagabine (Gabatril) extended survival, improved movement and lessened brain atrophy in the animals. Sertraline (Zoloft) had similar effects while it increased the protective BDNF growth factor. Both drugs worked at dosages in sync with human therapy. Call 410-614-0011.

Built-in biases—like looking only at clinic patients—skew studies on the nature of depression, says **Peter Zandi**. Recently, however, **his Hopkins team focused on data from the Baltimore Epidemiologic Catchment Area, an ongoing survey of mental illness in communities.** Women showed a higher risk for a first depression, with longer episodes and tendency for it to recur. About 15 percent of the first-timers had depressions they couldn't shake, even after 23 years. Roughly half, though, recovered and had no repeats. Call: 410-614-2686.

Closeness counts, says **Constantine Lyketsos**, on results of a study, with Hopkins and Utah State colleagues, on **patient-caregiver relationships and progression of Alzheimer's disease.** Patients whose caregivers felt emotionally close, especially a spouse, saw a beneficial cognitive effect on a par with some drugs used to treat AD. “It may mean the difference between staying home and going into care,” he says. Now, he adds, comes the search for the reason why. Call 410-550-0062.

**Almost all women who are illicit drug users keep smoking even though they're pregnant,** says **Margaret Chisolm**. But there's a bright spot: Given bupropion for their depression, pregnant, drug-dependent women in Chisolm's study also cut at least six cigarettes from daily use. That's far better than results with one of two other antidepressants or with no therapy at all. Bupropion has a good safety profile during pregnancy. Call 410-550-9744.

## A Decade Old and Doing Wonderfully, Thank You

*Road-testing a public health program for depression awareness is worth the effort.*

Taking a public health approach to depression is something that everyone in academia agrees is a good idea. But they hesitate at the how-to part. The immediate appeal of swallowing a pill will probably always trump putting better prevention in place despite long-term benefits of doing both.

Psychiatrist **Karen Swartz** and collaborators, however, have been both patient and determined. They also received unusually good advice when they set up Hopkins' ADAP—the Adolescent Depression Awareness Program—now a decade-old public health project to fight stigma and encourage treatment.

ADAP began in 1999 after a cluster of suicides in Baltimore high schools shocked nearby Hopkins as well as the communities involved. Swartz, with colleague **Sallie Mink** and others, stepped up to speak in the schools on teenage depression. But what they found shocked them. “We were troubled by how little people knew about depression,” says Swartz.

Fortunately, just as the Hopkins group was mobilizing to raise awareness, local corporate executives offered their strategic expertise. “They agreed with us about being proactive in pushing a school-based curriculum,” Swartz says. In fact, they encouraged a national program. “But we also heard, *don't rush this; do it in well-tested, pilot-studied stages.*”

Hastening a project involving thou-



“We want to change the way *all* students, their teachers and parents view adolescent depression, not just the kids who're suffering,” says director Karen Swartz.

sands of teens, widely varying school systems and possible untreated depression, however well-intended, has *danger* writ large. “Whenever funders or outside collaborators wanted to expand ADAP faster,” Swartz explains, “I was the cranky one who said no, we have to prove this first.”

Still, she says, the 10 years seem to have flown in developing a nationwide high school curriculum. It's one that teaches students how mood disorders are diagnosed and treated and why that's crucial. Among the program's tools are first-person videos that explore depression from both a teen's viewpoint and the parent perspective. “That the illness is treatable is our mantra,” says Swartz.

The program's content and approach have been tested and refined by the hot coals of feedback in local schools. “We learned we talked too much, for one thing,” says Swartz. Equal effort has gone into teacher training to enable the handoff from the clinicians who first taught ADAP. A mix of visiting medicos and teachers may ultimately be the way to go, though that, too, will be

tested. There's no question that students learn: Pre- and post-program questionnaires consistently verify that. Some 15,000 have been taught so far as ADAP has spread to 15 states and Washington, D.C. Yet the real fruit—to confirm it lessens stigma, suffering and teen suicide—still awaits harvest. That can happen, Swartz says, only after large-scale expansion and more intimate student tracking.

“I'd love to ask individual students how they respond to ADAP, if they've been depressed before. But we'd need parental consent for that,” Swartz explains, “and schools are more interested in having the curriculum than becoming our research partners.”

A new partnership with the National Network of Depression Centers—the nation's foremost academic depression programs—could help. It will widen ADAP's reach while it improves access to therapy for students who need it. Having the network on ADAP's side, Swartz says, may convince schools to support what she hungers for: studies that gauge impact. ■

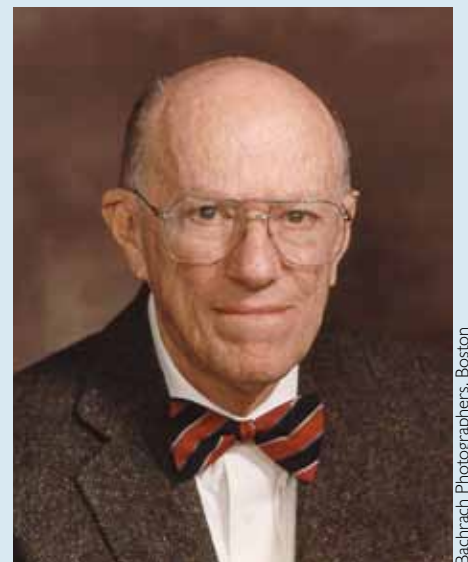
*For information: 410-955-0152*

## The Power of Perspective

Leon Eisenberg was often a voice crying in the wilderness. As a child psychiatrist at Hopkins in the 1950s and 1960s, his insistence on scientific rigor made him stand tall against that era's almost religious belief in Freudian psychoanalysis. Yet he equally bucked one-size-fits-all trends in biology-based therapy for the children he saw.

When he came to Hopkins in 1952, Eisenberg worked with Leo Kanner, dubbed “the father of autism” for defining the disease. Under Kanner, he completed the first long-term study of children with autism, work that's helped a generation of clinicians predict its severity. Eisenberg's exacting study of fathers of autistic children became ammunition for later genetic studies of the disease, though at the time it only diluted the popular “refrigerator mother” idea of autism's cause.

Ahead of his time in evidence-based care, he carried out the first randomized, controlled trials in child psychiatry. His studies of Ritalin, for example, brought a sea change in treatment for ADD, even though he was later deeply unsettled by its widespread prescribing. Eisenberg did seminal work on school phobia. And when Kanner retired, Eisenberg became chief of child psychiatry, holding the post almost a decade. The witty, kindly man died this fall. ■



Bachrach Photographers, Boston

Eisenberg was fond of asking at faculty gatherings, “Have you used your tenure to go up against the system?”

## Hopkins BrainWise

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