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NEXT issue The end

City of Secrets • Stemming Sickle Cell • End of the Road • A Stick in the Heart

Inflammation the body's friendly fire

Gravesite in Sri Lanka / Shehzad Noorani
“It could have been the flu, pink-eye, or hell, let me be stung by a bee. But Oh no, I was so lucky... I caught HIV.”

—From the poem “My Experience” by Tavon Vinson
Tavon Vinson just did not have time for this call.

The popular gay 18-year-old, class president of Edmondson-Westside High, an actor, an athlete … his life was too vital, too full, to have the gears suddenly stripped from an engine that loved running at full throttle. And yet the voice on the other end of the line was attempting to do just that. A doctor, an old friend, a comforting face that normally Tavon enjoyed seeing. But now, in this moment, in this context, he was disembodied, his tone somber, his words halting yet imploring. It was as though the cell phone was discharging volts of fear along with the message:

“Tavon… you need to come in.”
“My test, MY TEST! Tell me, TELL ME!” pleaded Tavon.
“I can’t. Not over the phone. Please, just come in and we’ll talk. It’s OK.”
“Look, I have a track meet to run tomorrow. It’ll ruin my focus if I don’t know. Tell me. TELL ME!”

This wasn’t a negotiation. The young man was desperate, consumed by dread. He’d always protected himself during sex. And he went for regular HIV tests. And he’d had no partners at all since his last test, so what was going on?

To the doctor, the cause wasn’t the immediate concern. The result was. It came down to compassion versus clinical guidelines. In the end, compassion won out. The doc couldn’t string this young man along, not for one more minute. And so, in a sentence, he forever changed the young man’s life.

“Tavon. The test. It … was positive.”

On the other end of the line, silence. Then screaming. Then cursing. And through it all, like a mantra against the torrent of pain, the doctor repeating, again and again, “I’m sorry, Tavon. I’m sorry. I’m sorry.”

The phone call ended. Tavon, in a daze, instinctively went to the place that had always brought him comfort. Across the field from his home was the track. As the sun set, he sat cross-legged on the infield, surrounded by the gravel lanes and chalked lines that had brought him glory.

And he cried.
And he cried.

The numbers have remained consistent and horrifying through eight years and three separate research cycles by Bloomberg School scientists and colleagues from the Maryland Department of Health and Mental Hygiene. According to the Behavioral Surveillance Research Study (BeSURE) sampling completed last December, 48 percent of African-American men who have sex with men (MSM) in Baltimore City are HIV positive. That’s far higher than the average of 28 percent found in the 20 other cities participating in the National HIV Behavioral Surveillance in 2008. (Researchers in Baltimore, like those in the other cities, recruited most MSM study participants from clubs and venues that might attract people who engage in higher HIV risk behaviors.)

The prevalence is even more troubling when compared to the two other cohorts in the BeSURE sampling: African-American MSM surveyed in 2011 were infected with HIV at a proportion more than three times that of injection drug users, and eight times that of heterosexuals considered at high risk for infection. Baltimore’s MSM community is, in one sense, a microcosm of a global issue; a recent Lancet article authored by Bloomberg School faculty noted that in countries like France, Australia, and the U.K., the overall HIV rate is declining in populations with the exception of one group: MSM.

In Baltimore, a key challenge for reducing HIV among the MSM community is testing. More than two-thirds of those surveyed with HIV had no idea they were infected prior to testing in the study. That means many African-American MSM are not receiving critical HIV care services, says BeSURE principal investigator Danielle German, PhD ’09, MPH. “It is also a challenge for preventing HIV transmission to partners,” she says. BeSURE participants “get the full scope of pre- and post-test counseling, referral services and linkage to care. That aspect of our activities is as much of a priority for us as the data gathering.”

BeSURE is working on the problem because there’s little doubt that knowing one’s status greatly lowers transmission risk. The transmission rate for people who know
At 49, Carlton R. Smith is old enough to remember when HIV was a death sentence. That it’s not anymore—at least for those who get tested and treated—is a message he conveys via the organization he founded in 2002, Baltimore Black Pride.

Consider the picture that Smith paints of the rejection a young, gay African-American male often encounters in the inner city. “It comes some out of the churches,” says Smith. “They preach out of the book of Leviticus that you’re an abomination. People who don’t have an understanding of the [religious] context hear that word and think they’re a blight on the planet. Sometimes, there’s a community sense of, ‘How dare you!’ You’re taught as an African American that you need to be a man and create and take care of your family. And now you’re going to come out and say you’re what? You’re gay?” — Carlton R. Smith

“You’re taught as an African American that you need to be a man and create and take care of your family. And now you’re going to come out and say you’re what? You’re gay?” — Carlton R. Smith

Some of the factors that impair self-esteem are not unique to the African-American community. But racism, poverty and high unemployment are endemic in the inner city. Access to resources—and even public transportation—is an additional barrier to testing and care. For many young men, the hurdles to determining one’s status, let alone accessing care, are too discouraging to consider. “When I talk to a lot of young people, they’re not worried about testing,” says activist Keith Holt, 26, who is HIV-negative. “They’re worried about living … ‘where am I staying at tomorrow? Will I have something to eat?’ It’s about what’s important to you at that moment. With HIV, it’s not something you think is affecting you right in the here and now, even though it is.”

And just as easily, discouragement can turn to anger, with deadly effects. “For people who have been kicked out of their house for being gay, or positive, or they can’t get insurance or medication or don’t know how to get it, they’re afraid they’re going to die, they’ve been through a lot,” says one HIV-positive community activist. “When you’re not getting help, and you have no one to talk to and you’re dealing with it by yourself … there’s a reason that people go crazy and have unprotected sex. They just don’t care anymore.”

And so the wildfire continues to rage.

For those on public health’s frontlines, spreading the test-and-treat message among Baltimore’s African-American MSM community is no easy task. That may be due to a lack of urgency on the part of younger MSM, who haven’t seen their peers die from AIDS in the numbers that older MSM have. Another barrier is that the African-American MSM community is so fragmented that an outreach effort or a single ad campaign is unlikely to reach all MSM.

“The conundrum of programs since I’ve worked in them here, in Seattle and New York, is that when we say we’re having a ‘gay’ event, we get men who identify as gay and it’s usually white or Asian gay men who make a certain amount of money,” says Anthony Morgan, an HIV health educator with the Lighthouse, a Bloomberg School project that conducts community-based disease reduction research and education in Baltimore. “And when you look around the room you notice that maybe there’s one or two Latino guys, and maybe a black guy. So do you say we’re just having a black men’s program, and see who is engaging in a certain type of sex? Do you say ‘MSM’ and risk that no one will connect with it? Or is that term too objectifying; does that just reduce you as a human to where you put your penis?”

There’s no shortage of groups that fall under the MSM banner. There are the out and open, who may well be in the minority; these include the club-goers who were recruitment targets of BeSURE’s cohort, and members of the ballroom scene, where “houses” compete in lavishly costumed and elaborately produced shows reminiscent of French haute couture runways.

But many African-American MSM lead fully or semi-closeted lives: professionals, college students, bisexuals, men on the
“Isn’t this some shit, 
I’m track captain, president of my class, 
But now everybody won’t see that, 
just the gay black boy 
that’s gonna die fast.” —From the poem “My Experience” by Tanen Vinson
"A dear friend became positive, and he never knew until he had full-blown AIDS. It changed my life, and got me out in the community to get people tested."
—Adrian Ross
“down-low” who meet regularly for sex with men in a tight-knit group that is never mentioned elsewhere. These groups are far harder to reach. In some cases, the reticence to discuss homosexual sex is so pervasive, it’s not even acknowledged by men who engage in sex with men as part of their work.

“One focus group we did was with men who sold sex,” says Latkin, an HBS professor. “And one guy brought in [male prostitutes] from The Block where they sold sex. What I found fascinating about that discussion was that here were six guys who knew each other, and nobody ever mentioned having sex with a man; they might say ‘a client,’ or ‘somebody,’ or this and that, but even in a group that was completely aware of each other’s behaviors, there was still a high level of stigma, of even talking about [MSM] for that group.”

Given this ongoing reluctance to self-identify sexual preferences or which subgroups one identifies with, behavioral interventionist Karin Tobin, PhD, says the best course might be to focus on education. She and Latkin have been piloting a program called Unity in Diversity, which targets African-American MSM (including MSM who also sleep with women) to educate them about their status, risk behaviors such as frequency of condom use and, most importantly, to encourage them to pass that information on to their social networks regardless of how they self-identify.

Tobin reports that three months after the seven group meetings, participants reported a reduction in the number of male sex partners and an increase in condom use compared to those in the control group, which had just a single risk-reduction counseling session. But what also caught her ear was how participants didn’t readily verbally identify with being gay or part of an MSM subculture. “In our experience with guys in Unity in Diversity, if we don’t bring it up, they’re not bringing it up. I’m not going to force a label on anyone,” says Tobin. “I think folks come in waiting for that shoe to drop, for you to put a label on them. And even if someone were to think, looking from the outside, that a person identifies as gay, he may never use the term, ‘I’m a gay man.’”

Activist Adrian Ross, 26, agrees that a simple, broad test-and-treat message is probably best: “Take a message targeted to the ballroom community. What is a D.L. [down-low] or ‘straight-identifying’ [MSM] going to know about the ballroom scene? Nothing. What he does, he does in the dark, fast and quick.”

Whether Tobin’s efforts have a long-term effect on Baltimore’s MSM HIV crisis remains to be seen, but what all sides agree on is that any inroads will need tremendous community buy-in. Identifying and gaining the trust of the key stakeholders is where the game is really at. MSM are taking leadership positions in the community for their friends and other young men who need support.

In Baltimore, being educated, tested and treated for HIV is a hit-or-miss proposition. The city’s school system barely touches upon the subject. For the inner-city African-American MSM community, comprehensive, one stop test-and-treat shops sensitive to their issues are hard to find. Single-focus, free clinics can be so obvious that to be seen there is the scarlet-letter equivalent of saying, “Oh … you, too.”

It’s no wonder Latkin says, of the overall academic, city and state public health push to engage the African-American MSM community in HIV awareness, there’s no coherent plan. “There’s inadequate monitoring of what’s going on in the community. We don’t know when people drop through the cracks,” says Latkin. “If someone is treated at Hopkins but then goes to University of Maryland, we don’t know, they may be lost. Maybe there’s too much testing in the community and not enough linkage to care. Or maybe one group has been inundated with [‘get tested’] messages and another hasn’t gotten a message in months. It’s completely fragmented, how we approach it, and this leads to huge inefficiencies and lack of effectiveness.”

Acting Baltimore City Health Department deputy commissioner Patrick Chaulk, MD, MPH ’89, says the city is doing its utmost to provide testing and care. As in other U.S. cities, individuals who receive a positive diagnosis at a Baltimore City health facility are referred to a care provider. “But we take it a step further; if you get diagnosed we have same day referral in which we drive you to a provider, wait for you to get everything done, and then drive you home,” says Chaulk. “We do two of those visits in the first six months [after an HIV diagnosis]. I don’t know of any other city that does that.”

Still, with Baltimore missing a major grassroots African-American MSM-oriented organization like Washington, D.C.’s Us Helping Us, the movement to bring a message of hope and cohesion to those most at-risk has landed squarely on the shoulders of those with the most energy and awareness: the city’s African-American gay youth.

Before he could become an AIDS activist, Tavon Vinson first had to survive the emotional plunge following his diagnosis. Vinson and his doctor believe he was infected by a contaminated needle during

They’re not worried about testing. They’re worried about … "Where am I staying at tomorrow? Will I have something to eat? With HIV, it’s not something you think is affecting you right in the here and now, even though it is.”

—Keith Holt
Tin Tun rides his motorbike through the Thai border town of Mae Sot.

He cruises past rice fields on the outskirts until he reaches the warehouse of a corn-processing plant. A wiry man with a broad forehead and receding black hair, he ducks into a passageway that leads to an encampment for Burmese migrant workers. Tin Tun must travel here each week to counsel Yi Yi (not her real name) because she is afraid to leave the workers’ compound. Like other undocumented Burmese, Yi Yi fears the Thai police, who often demand bribes to ignore migrants who lack the proper papers.

Tin Tun’s counseling session is part of a study by the Bloomberg School’s Applied Mental Health Research (AMHR) group. Its aim: to test whether lay counselors with brief training and close supervision can provide effective therapy to people within their communities who have suffered from trauma or violence.

For Yi Yi and the roughly 2 million other Burmese who have crossed into Thailand, harrowing stories are commonplace. Since 2011, a quasi-civilian government in Burma (also known as Myanmar) has eased repression. However, these reforms follow on nearly 50 years of military rule that gutted the economy, outlawed dissent and waged war on ethnic groups seeking self-determination. The junta packed the prisons with dissidents.

The army burned thousands of villages, destroyed crops and forced people to do
Joe Cepeda

“Can we make therapeutic interventions that work?
Can we train people who don’t have a mental health background to provide them?”
—Paul Bolton

dangerous work without pay; Tin Tun’s colleague Mya Mya Win, for example, counseled a woman whose brother died doing forced labor.

Tin Tun himself has faced prolonged hardship. He was arrested for political activities the day after his daughter’s birth. Torturers deafened his right ear and scarred his body.

When the regime released him in 2009, his baby daughter was 19 years old.

Today, it is Yi Yi’s suffering that he will address. Tin Tun walks down the trash-strewn lane between two rows of houses pieced together from bamboo, corrugated zinc, plastic sheeting and empty rice sacks. Yi Yi emerges into the glare to greet Tin Tun.

She is 45, has short black hair and dresses in stylish capris. Tin Tun kicks off his flip-flops and stoops to follow her into the wobbly 8-by-10-foot shack with a roof made of leaves. He sits cross-legged on a woven mat facing Yi Yi, and they begin to talk.

The purpose of therapy with Yi Yi and others is to help them recognize the connections between thoughts, feelings and behavior and to use this understanding to feel better. In eight to 12 sessions, Tin Tun and 16 other counselors teach their clients to notice negative or self-defeating thoughts and behaviors and then to reconsider them. The counselors guide clients in moderating their intense emotional and physical reactions to memories of trauma.

More is at stake than the clients’ psychological distress: depression and anxiety can lead to physical illness, risky behavior, fractured relationships, injuries, lost wages, even suicide.

Today Yi Yi talks to Tin Tun about her divorce. She thought it was all her fault, but Tin Tun has helped her see that her husband’s drug addiction played a role. When Yi Yi began therapy, she recalls, “I felt so hopeless. I had no future.” These days, she says, “I have many goals.” Each day, she and her new husband manage to spend only $1.50 of the $5 to $7 he earns loading trucks. “When we go back to Burma, we can open our own rice shop in Yangon,” she says.

Another of Tin Tun’s clients was a young man who was furious with his father for the political activism in Burma that landed him in jail. The son felt abandoned. Tin Tun says he helped his client to recognize that the father had been attentive before his imprisonment, and that after his release, the father had helped his son to find work in Thailand. At the start of therapy, the young man “felt as if a stick was stuck in his heart,” says Tin Tun. “Now he feels he can take out the stick.”

Tin Tun’s own children refuse to see him because they resent his absence while in prison. To avoid obsessing over his grief, Tin Tun applies to himself the coping skills he teaches to his clients. He redirects his thoughts and seeks positive interpretations for events.

Tin Tun’s supervisor, Kyaw Soe Win, and his colleagues learned a structured method of counseling from assistant scientist Laura Murray, PhD. She and two colleagues spent two weeks in Mae Sot in early 2011 training the counselors, mostly high school or college graduates.

Research is scarce regarding the mental health of Burmese in Thailand, but two studies, one of ethnic refugees and one of exiled dissidents, both found that four in 10 were depressed. Among the dissidents, one in four had PTSD. The Thai health care system provides little in the way of counseling, and Burmese without papers generally don’t feel safe going to a government clinic.

The project in Thailand is one of eight linked studies in Asia and Africa under AMHR’s aegis. The research, supported by the USAID Victims of Torture Fund, tests strategies for using local counselors to help people with problems such as anxiety or depression stemming from extreme poverty, trauma or systematic violence. Other study sites are in Zambia, the Democratic Republic of Congo and Iraq.

In all eight studies, “the principle is always the same,” says International Health associate scientist Paul Bolton, MBBS, MPH ’93, MSc, the group’s leader. “Can we make therapeutic interventions that work? Can we train people who don’t have a mental health background to provide them?” The unmet need is stark: a 2011 *Lancet* commentary reported that more than 75 percent of people with neuropsychiatric problems in poor countries get no treatment. To help fill that gap effectively, says Bolton, researchers must first test interventions through randomized studies like these.

So far, he says, results in all sites show that most people in the communities accept counseling and that “task-shifting” works: that is, paraprofessionals like Tin Tun can learn to conduct it correctly. But do the therapies help the clients themselves? Bolton says it’s too early to judge.

The Thailand study, led by International Health assistant professor Courtland Robinson, PhD ’04, and doctoral student Catherine Lee, took unexpectedly long to enroll 154 clients and 131 controls (who can get free counseling after waiting 10 weeks).

Counseling for people without severe psychiatric illness is virtually unknown in Burma. As Kyaw Soe Win explains, “Most people think counseling is for people who are crazy. I finally got the idea of telling the community, ‘If you were crazy, we couldn’t give any counseling to you.’ ”

Ultimately, he and several other counselors want to return home and provide therapy in Burma if the recent reforms prove to be genuine and lasting. “Many prisoners have been released, and they have been tortured,” says Mya Mya Win. “I want to counsel them.” Among the ex-prisoners are two of her own sisters.

Meanwhile, Kyaw Soe Win says he will look for money to keep counselors working in Mae Sot after the Hopkins study closes at year’s end. “I’d like to do this for the migrant community,” he says. “They have faced so much suffering.”

Cathy Shufro reported from Thailand this spring on a fellowship from the International Reporting Project, an independent journalism program in Washington, D.C.
FRIENDLY FIRE
A new wave of research links inflammation to almost all chronic disease

Story Maryalice Yakutchik
Illustrations Michael Glenwood

The inflammatory system is like the ocean. It’s beautiful, but also deadly. —Josef Coresh
“It’s not simply the presence or amount of inflammation that’s important. It’s the texture of it. That’s where you find the causes of diseases.”

— Noel Rose

Sixty years ago, Patricia Mabe took her first-ever breath, inflating new pink lungs with the air of Carbondale, Pennsylvania, home of the nation’s first underground mine; a town that today, despite a long-ago demise of the anthracite industry, still smolders from burning veins of coal.

Mabe’s subsequent inhalations—even before she acquired, at age 15, a smoking habit that would be lifelong—no doubt contained vestiges of a variety of toxins, no matter whether she was outside or in. Her dad, who worked in a mine, was a smoker. Her mother smoked, too.

Whenever Mabe inhaled anything noxious, her body’s defense system recognized foreign molecules in her lungs as the interlopers they were and mounted a functional inflammatory response. Brawny cells called macrophages, among others, stormed her lungs to do away with pathogens and debris while unleashing a barrage of molecular messengers that orchestrated strategic battles and mended damaged cells.

Then—and this is every bit as important as their SWAT-team-like arrival—the macrophages would leave with all their assorted artillery in tow once the mission was over. In a healthy system, inflammatory cells are both highly regulated and self-disciplined; they go where ordered, expertly distinguish friend from foe, exert only necessary firepower, tidy up after themselves and then retreat, ultimately restoring calm—also known as homeostasis.

Precise though the immune system may be, some level of self-attack occurs even when all parts are working well. The key is keeping the collateral damage in check.

In fact, how effectively and efficiently any one person controls inflammation is a key determinant of health and disease. Some individuals regulate inflammation better than others. It’s likely that many of us are able to control inflammation at certain times of our lives better than at other times. Why—and how—is the focus of intriguing research that’s implicating how nutrition and inflammation interact in just about every major chronic disease.

“There appear to be windows of opportunity when we are good at adapting to what is in our environment, which is intimately related to how we meet and greet and defend ourselves from potential invaders,” says Keith West, DrPH ’86, MPH ’79, the George G. Graham Professor of Infant and Child Nutrition. “We get less good at that as life goes on.”

Over time—likely in response to the toxicity and persistence of cigarette smoke in her lungs—Mabe’s inflammatory response turned pathological. The composition of immune molecules and cells became qualitatively and quantitatively different. Inflammation became too too: There was too much of it; it was too strong for too long.

Complicating that scenario, macrophages also became unfaithful and lingered incompetently in her lungs, clogging her airways.

What once defended her from disease now was causing it.

There’s a new buzz among scientists about inflammation, even though it’s been known for ages to be one of the first responses by the immune system to infection and irritation. Inflammation is hot. And not in just a classical “calor” kind of way. Calor—as in heat or fever—is one of four characteristics of inflammation recorded in De medicina, an ancient Roman medical text. The remaining three—dolor, rubor and tumor—translate to pain, redness and swelling, respectively.

“Inflammation is something we have rediscovered in the 21st century,” explains Shyam Biswal, PhD, MS, a professor in Environmental Health Sciences (EHS), “specifically, inflammation as a focal point of chronic disease. People used to think of it as a bystander of disease. But it’s actually a driver.”

If attention to inflammation is spreading like wildfire throughout the research world, an early spark was ignited by Noel Rose, MD, PhD, director of the Center for Autoimmune Disease Research. Having introduced the concept of autoimmunity as a cause of chronic thyroiditis in 1956, Rose now is investigating the causes of magnified inflammatory responses in the hearts of young men for whom transplant is the only cure. A muscle that needs to pump, Rose concedes, is a bad location for excessive scarring to occur as a result of inflammation.

“We’re now looking at the details of inflammation,” he says, “and realizing the benefits from targeting specific parts of the inflammatory response. You have to know which part is doing good and which is doing bad and tailor drugs accordingly.”

It’s not simply the presence or amount of inflammation that’s important, Rose says: “It’s the texture of it; the makeup of the cells that are attracted, the ways in which they are stimulated and the products they release. If you’re getting down to that level, that’s where you find the causes of diseases.”

Among chronic, noninfectious disorders now commonly regarded as “inflammatory” is atherosclerosis, often called hardening of the arteries, says Josef Coresh, MD, PhD ’92, MHS ’92, director of the George W. Comstock Center for Public Health Research and Prevention.

“We’ve known for a long time that inflammation is central to atherosclerosis,” says Coresh, principal investigator of the Johns Hopkins Field Center of the Atherosclerosis Risk in Communities (ARIC) study. “You can see inflammatory cells in the lesions.” (Known as plaques, lesions form in the arteries, hardening them.)

The prospective ARIC study, which first examined 15,792 Americans in 1987 and has followed them ever since, is a key resource for the investigation of many inflammation-related chronic diseases—few of which show their hands so obviously as atherosclerosis.

Researchers who are sleuthing the origins of cancers and diabetes, for instance, have found themselves stumbling time and again on inflammatory roots. Apparently, long ago resolved and seemingly unrelated infections buried deep in people’s pasts might tip the precarious immune system balance, imperceptibly if irrevocably reprogramming it. So too might the persistently simmering, subclinical kind of...
inflammation caused by excess body fat, for example. One investigative focus is finding the mechanisms that link long ago infections to inflammation and later, chronic diseases. Another is dissecting and tinkering with processes that can block, enhance or otherwise regulate inflammation once the SWAT team has mutinied.

For instance, Andy Pekosz, PhD, with collaborators from Johns Hopkins Medicine, has demonstrated that epithelial cells harvested from the noses of patients suffering from chronic sinusitis “remember” many generations later that they are different. These cells have comparatively heightened inflammatory responses to various stimuli a month after leaving a diseased nasal environment—despite having been grown and propagated under the same conditions as healthy cells in lab culture dishes.

“This tells us something about these cells that has changed,” explains Pekosz, an associate professor in the W. Harry Feinstone Department of Molecular Microbiology and Immunology (MMI). “The detection machinery or the circuitry in the cells from sinusitis patients is reprogrammed to respond differently to factors that stimulate inflammation.”

Understanding this reprogramming of the inflammatory response itself is the holy grail for Pekosz.

“If we could understand how to turn down that heightened response by the epithelial cells, we could relieve the chronic sinusitis,” he says. “The flip side is, if we could, at an opportune and early time point, find a way to increase the inflammatory responses, we might have a very powerful broad tool to use against a number of different viruses, for instance.”

Fiddling even a bit with any discrete part of a delicate and complex system is not without unforeseen consequences, many of which could be perilous, if not immediately, then sometime in the future. (Case in point: Although it provided sweet relief for many with osteoarthritis pain, the anti-inflammatory drug Vioxx, which works by inhibiting an enzyme in the inflammatory pathway called COX-2, was withdrawn from the market in 2004 after a study showed it doubled patients’ risk of heart attacks and strokes after 18 months of use.)

The inflammatory system is like the ocean, according to Coresh: “It’s beautiful, but also deadly,” he says. “As long as it’s calm, you can conduct commerce and fish on it, and without it, you’re dead. But, if it storms, it’s incredibly powerful and can kill you.

“When there’s imbalance in one thing, it’s like a wave that pushes on other things and you get a whole cluster of effects.”

**AMONG THE “THINGS”** that both cause and react to system imbalances are messenger proteins called cytokines. The immune system communicates through these versatile factors that float around in the bloodstream. Unlike neurons in the hard-wired nervous system, cells in the immune system are not physically connected to one another.

“If you think of the nervous system as a landline, then the immune system is a cell phone,” says Jay Bream, PhD, an MMI associate professor. “Different cocktails of cytokines, in various abundances, play a central role in determining immune responses.”

A phenomenon known as a “cytokine storm” can occur if the reaction of the immune system to a pathogen is wildly exaggerated and stimulates too many of the messenger molecules, which in turn activate the same cells that stimulated them, resulting in a dangerous feedback loop. For example, cytokine storms are associated with severe bacterial infections and the onset of septic shock as well as avian influenza (H5N1) infection. Likewise, infection with the deadly Ebola virus is associated with a cytokine storm leading to uncontrolled inflammation.

Cytokine storms can happen in tissues throughout the body. That’s because the component parts of the immune system spread far and wide, from the top layer of skin to the deepest recesses of the bowels.

Bream, whose mission is linking cytokines with disease outcomes, studies Interleukin-10 (IL-10): “a lynchpin” he says, “at the nexus of inflammation.”

When the volume of IL-10 is turned down low, inflammation happens. When it’s blasting, inflammation is tamped down. Bream, co-director of the Becton Dickinson Immune Function Laboratory at the Bloomberg School, has shown that mice prone to express higher levels of IL-10 are susceptible to certain types of persistent infections because they can’t mount appropriate inflammatory responses. If there’s an under-abundance of IL-10, they are susceptible to immunopathology caused by collateral damage from the excessive immune response. In this scenario, the original infections clear, but the animals’ inflammatory responses set them up for autoimmune diseases and cancers.

Some people get colds and can go to work while others are bedridden. It’s this diversity in the human population of response to disease threats that is at the center of my research program.”

To find out why some individuals control inflammation better than others, he’s
looking at tiny genetic variations (known as single nucleotide polymorphisms, or SNPs) that make each human a unique individual, and noting how they affect the levels of IL-10 in various tissues, ultimately exerting control over inflammation and disease.

Because he wants to know how IL-10 works in people, Bream has inserted chunks of DNA containing the human IL-10 gene into the mice he’s using. Some mice get human genes with variations associated with high IL-10 expression, and some get human genes with variations associated with low IL-10 expression.

Among other things, he’s discovered that location is all-important: Where he manipulates IL-10—that is, which tissue type—matters. If, for instance, Bream turns down the IL-10-producing ability of a subset of cells in a very specific area of the colon, just below the surface cell layer, those mice end up with severe colitis.

“IL-10 is an attractive target for therapeutic interventions that either add back or neutralize IL-10,” says Bream, who’s now testing different expression levels of the human gene across various tissue types in response to different kinds of infectious pathogens in mice. “By identifying the triggers and genetic variations that regulate IL-10 levels, it will be feasible to develop more personalized therapies that restrict or enhance IL-10 in tissues where inflammation is occurring. But it’s extremely complicated.”

Another group of researchers at the Bloomberg School is looking at the anti-inflammatory IL-10 cytokine in the context of frailty in older adults. Some elderly people get frail in a clinical sense, meaning they spiral into a vicious cycle of decline characterized by exhaustion, slowness, weakness and muscle loss.

“It’s hypothesized that there’s at least a subset of older adults in whom inflammation essentially gets turned on all the time,” says Karen Bandeen-Roche, PhD, the Frank Hurley and Catharine Dorrier Professor and Chair of Biostatistics, and co-principal investigator of the Older Americans Independence Center. “It’s associated with muscle wasting and other adverse outcomes.”

Bandeen-Roche is collaborating with Jeremy Walston, MD, a Johns Hopkins professor of Medicine and co-director of the Biology of Healthy Aging Program, who has developed a frail mouse model by knocking out expression of the IL-10 gene.

“In human studies, again and again, associations of high inflammation and adverse outcomes have been revealed, with frailty prominently among them,” says Bandeen-Roche. “Pro-inflammation is thought by many to be one of the key hallmarks in a cycle of multisystem dysregulation that leads to frailty.”

Human studies designed to discover how inflammation works and reveal its links to diseases require not only big funding and endless approvals but also plenty of participants, willing subjects who are healthy, as well as those who are sick.

People like Patricia Mabe, for instance.

FIVE YEARS AGO, Mabe visited her doctor complaining of asthma-like symptoms. Disconcerting as that was, it didn’t affect her everyday life. An inhaler was prescribed, and for a while, she used it only occasionally. Then, two years ago, it was like a switch had flipped.

“I was always very active—some people might say hyper,” she says. “Then, all of a sudden, I didn’t have any energy.”

An avid walker, Mabe grew depressed when she couldn’t exercise with Buddy, her Yorkshire terrier, and Holly, her English bulldog. Already petite, she lost weight, falling to an alarming 86 pounds.

Quite a few members of Mabe’s extended family had breathing issues. Her
"Our discovery is not restricted to lung diseases only. If this pans out, it could be a big thing for public health.”

—Shyam Biswal

parents, both lifelong smokers, needed course after course of antibiotics to fight recurring infections before they died, one year apart, from chronic obstructive pulmonary disorder (COPD). Given her heredity and behavior—despite attempts to quit, Mabe still smokes—she envisioned a bleak future. COPD is an umbrella term that includes chronic bronchitis, emphysema and chronic asthma or asthmatic bronchitis. Most people have a little of this, a little of that, according to Robert Wise, MD, a Johns Hopkins School of Medicine professor of Pulmonary and Critical Care Medicine who holds a joint appointment in EHS at the Bloomberg School. All suffer declining lung function that can contribute to coughing, panic and death. COPD has no cure. Although smoking is a major risk factor, only one in seven smokers ends up with the disease.

Why Mabe’s parents? Why her?

Eager for answers, Mabe signed up for a research study investigating the link between genetics and COPD. More recently, she participated in a clinical trial instigated by Shyam Biswal’s research involving a new therapeutic agent: sulforaphane, a compound from broccoli sprout extract that was discovered in 1992 by Paul Talalay, MD, a professor in Pharmacology and Molecular Sciences who has a joint appointment in International Health at the Bloomberg School.

If scientists can prove in this study and successive clinical trials that sulforaphane works in people—like they previously demonstrated it worked in mice and in human cells in a dish—they will have found a potent intervention for a largely ignored public health issue affecting millions of Americans. (COPD is the No. 3 cause of death nationwide.) In addition, billions of people worldwide also might stand to benefit, mostly women and children whose lungs are chronically compromised from indoor air pollution caused by cooking fires fueled by cow dung and brush.

Sulforaphane works differently than existing anti-inflammatory agents, Biswal explains. Rather than tamp down inflammation by interfering with its various pathways, it ramps up a host’s defense system that’s been compromised by chronic inflammation. It breathes new life into Nrf2, a vital molecular player that’s effectively strangled by the “bad” inflammation that underpins not only COPD but also nearly every chronic disease imaginable.

Already, Biswal’s group has published research demonstrating in the lungs of COPD patients that a defect in the host defense results from a decrease in Nrf2.

Additionally, they have shown that sulforaphane boosts Nrf2 levels and this enhances host defense in the lungs by improving the ability of macrophages to kill bacteria and making them more responsive to anti-inflammatory drugs such as steroids.

The ongoing clinical trial in which Mabe participated is double-blind, meaning that nobody knows yet whether their purple pills are placebos or contain high or low doses of broccoli sprout extract. But Mabe has a sneaking suspicion that she ingested sulforaphane and that it helped her. During the month-long trial when she dutifully swallowed her pills daily, she felt different. “It seemed like my air passages opened up more,” she reports. “I didn’t have any flare-ups during that time, and it’s odd that I wasn’t on my nebulizer for a whole month.”

The multicenter trial, coordinated here at Johns Hopkins and taking place at Temple University and SUNY Buffalo, to date has enrolled about half of the 90 participants needed to test whether feeding sulforaphane to people alters Nrf2 activity as assessed by anti-oxidant enzymes in macrophages. Reducing inflammation is ancillary.

“If we can’t hit this target, then we’ll have to step back and say, well, this works great in mice and in the test tube, but not when people ingest sulforaphane,” says Wise, who’s heading up the broccoli sprout extract clinical trial.

This wouldn’t be the first inflammation-related wondercompound to fall apart in a human trial. But Wise is confident in the predictive quality of Biswal’s previous research. In addition, others have shown Nrf2 was increased in the nasal tissue of people who eat broccoli sprouts.

“We think if you can show that in the nose, we can show it in the lung,” Wise says.

That this strategy potentially may benefit nonsmokers who have chronic inflammation in the lungs is notable in the context of public health. Not incidentally, the WHO lists indoor air pollution from primitive household cooking fires as the leading environmental cause of death in the world.

“There’s no question that women and children in South America, Africa and South Asia are exposed for many hours a day in cooking huts to amazingly high levels of particulates from burning biofuels like cow dung, and that this leads to a condition that is akin to COPD,” Wise says. “They develop chronic cough and mucus production. They have airflow obstruction and die early.”

How their lungs are similar to or different from those compromised by tobacco-related COPD is unknown, prompting Biswal to remain hot on the Nrf2 trail.

Currently, he’s implanting particulate collected from cooking huts in India into the lungs of mice and testing how manipulations of the Nrf2 pathway affect disease outcomes. Next, he’s working on developing a breathing chamber for mice that would be analogous to the interior of a cooking hut.

“Our understanding is very weak in this area,” Biswal says, “and half the world’s population is at risk.”

If sulforaphane does, in fact, tackle COPD by boosting the defense system and rendering the immune system once again competent, complete with robust macrophages, what’s to prevent it from doing the same for those suffering from a gamut of inflammation-related diseases, including cystic fibrosis, HIV, cancer, asthma, psoriasis, sepsis, schizophrenia, atherosclerosis …?

“Nothing,” says Biswal. “Our discovery is not restricted to lung diseases only. If this pans out, it could be a big thing for public health.”
Shared vision: Srinivasan Chandrasegaran (left) with Sivaprasad Ramalingam
A few months back, Sivaprakash Ramalingam, PhD, focused his microscope on a crowded clump of human stem cells and saw a reddish glow—a chemical signal he had successfully inserted a gene into a “safe harbor” site in the cells’ DNA where it wouldn’t interrupt vital functions.

It was a crucial step in a drive by the postdoc and his advisor, Environmental Health Sciences (EHS) Professor Srinivasan Chandrasegaran, PhD, to develop a practical cure for sickle cell disease. The painful and debilitating genetic illness affects millions of people around the world, including in the U.S. and some of the poorest regions of India.

Ramalingam, 34, began his life on a small plot of land near the Bay of Bengal in southeastern India. While his father toiled in the family’s banana grove, sugar cane field and rice paddy, young Siva helped out by milking the family cow.

Today, Ramalingam works with his mentor Chandrasegaran—also a native of the southern Indian state of Tamil Nadu—on the frontiers of genetic medicine, trying to find gene-based cures for major health challenges like cystic fibrosis and HIV, as well as sickle cell disease. In their common quest, it’s hard not to see a torch passing from one generation of
scientists to the next, from basic science to applied medical research and from Western institutions to young researchers from the rapidly advancing scientific institutions of the developing world.

The two public health scientists are collaborating with stem cell expert Curt I. Civin, MD, of the University of Maryland, on the sickle cell project. They are racing with labs around the world pursuing similar goals. In May, the Maryland Stem Cell Research Fund awarded Ramalingam one of 17 grants worth up to $200,000 over the next two years for his sickle cell work, as part of a program to support Maryland scientists pursuing novel approaches to stem cell therapies.

Ramalingam and Chandrasegaran say the painstaking research could take two or three more years before it is ready for testing in animals, in preparation for human trials. Asked whether they worried about the intense competition, Ramalingam admits that he sometimes loses sleep over the publication of an important paper by a rival lab.

Chandrasegaran just smiles. The 30-year veteran scientist, who pioneered the development of man-made gene-editing tools called zinc finger nucleases, takes a philosophical approach. “If you’re asking me, do you want to be first? Yes. But it’s not in our hands. If others do it, we will be happy that it was done since it will help a lot of people,” he says.

There is no guarantee of success in this latest assault on the scourge of sickle cell. Except for mice and yeast, the DNA of most animals, including humans, is notoriously difficult to fiddle with and many efforts to repair human genes have failed.

Some early gene therapy patients died when viruses carrying engineered DNA inserted it at random locations on the genome and switched on genes that caused cancer.

Chandrasegaran says he’s leery of overselling his lab’s progress. “I want to keep it low-key,” he says. “Let’s take it one step at a time, and do careful science.”

But for Chandrasegaran, as for many other scientists, the relatively recent discovery that stem cells can be “induced” or derived from adult cells has opened exciting new avenues for medical research. “I hope that I can see it in my lifetime,” he says. “I’d like to see people cured of HIV, cured of sickle cell—any monogenic disease where you can replace the cells. It will help a lot of people, and that’s the ultimate goal.”

Death’s Crescent
Sickle cell is among the most common disorders caused by a single genetic defect, and it can be devastating.

People with the disease produce crescent-shaped red blood cells that are stiff, sticky and prone to piling up or breaking apart, clogging small vessels. These misshapen cells only live about one-tenth as long as normal blood cells, and a patient’s bone marrow can’t make replacements fast enough to keep delivering sufficient oxygen to the body.

Clogged vessels often trigger attacks, called “crises,” that produce acute pain in the back, chest, arms or legs and can last for hours or days. Patients may suffer leg ulcers, small strokes, blindness, and kidney failure and be prone to lethal infections.

The disease is found in certain populations around the world but is most common in Africa, parts of the Middle East, India, Central America and the Caribbean. It affects an estimated 90,000 to 100,000 people in the U.S., including about 1 in 500 African Americans.

The mutation that causes the disease is thought to have evolved in the tropics. For those carriers of a single gene (said to have “sickle cell trait”), most do not have symptoms of sickle cell disease but do have some protection against malaria.

In the U.S., the universal screening of newborns and early, aggressive treatment of sickle cell disease with blood transfusions, antibiotics and other drugs have helped reduce infant mortality and prolong lives. But the disease can still have a devastating impact on patients: Life expectancy in the U.S. for women with the disorder is still only about 48 years. For men, it’s 42.

In recent years, doctors have cured sickle cell disease in a few hundred patients using a technique that combines stem cells from healthy donors with bone marrow transplants. But the procedure is expensive and risky, Chandrasegaran says, while matching patients with healthy donors can be very difficult.

So Ramalingam and Chandrasegaran, working with Civin, are trying a different approach. Instead of using donors, they plan to take a sickle cell patient’s own stem cells, repair the faulty gene, and turn the repaired stem cells into blood and blood-producing...
cells. The hope is that these healthy cells, put back in the body, will outlast and replace the diseased ones without the need for a bone marrow transplant.

The aim is to make the repair of a patient’s sickle cell gene safer, simpler and cheaper, putting the procedure within the reach of more patients. “We’d like everybody to have access to it, so we want to make it as inexpensive as possible,” says Chandrasegaran.

If the technique works, the senior researcher says it could have wide applications. The biotech company Sangamo Biosciences of California has licensed some of Chandrasegaran’s work and is using a similar strategy to knock out a gene known as CCR5 with zinc finger nucleases, eliminating a route HIV uses to invade and hijack the body’s immune system.

The Mentor Chain
When he was still in India, Ramalingam, who earned his doctorate in molecular biology from the University of Madras, studied strategies for boosting the iron content of rice through manipulating the crop’s genes.

That’s how he heard about Chandrasegaran’s groundbreaking work on zinc finger nucleases, called ZFNs, as a tool for tweaking DNA. “Chandra was the expert,” the younger scientist says. “I sent him my CV and wrote that I was interested. I was very fortunate to work with him.” He came to Hopkins in 2008 as a postdoc to work with Chandrasegaran in EHS.

One advantage of ZFNs and similar gene-editing technologies, Chandrasegaran says, is that, made carefully, they can be targeted at one and only one point in the genome, avoiding the damage that can be caused by random insertion. (Sickle cell disease is caused by an error in a single chemical “letter” in the 3.2-billion-letter-long library of human DNA.)

But making these precise tools for cutting and editing DNA isn’t always simple. Ramalingam says he probably faces another two or three years of working on this crucial phase of the effort. “The success rate is very, very low here,” he says. “So you need a lot of patience doing this research.”

The postdoc, who is married with a 10-month-old son, says he was very proud when his parents traveled the 7,000 miles from his tiny home village of Kullampalayam to visit the Baltimore lab. “They were very excited, they were very happy,” he says. “I tried to explain it to them and the basics, they understand. But the technology, they may not yet.”

While the sickle cell project could accelerate Ramalingam’s career, his senior partner in the lab is considering retiring after three decades at the School. Chandrasegaran, who grew up as one of 10 children, is the son of a customs official working in what was then the French colonial city of Pondicherry on the Bay of Bengal. Accepted to an elite state-run military secondary school, Chandrasegaran rose to the rank of house captain, excelled at physics and graduated with honors. “All my friends who right now are in India? They’re generals and air marshals,” he says.

But he decided to become a scientist rather than an officer, earning a degree in chemistry from the University of Madras in India and his doctorate from Georgetown. He came to the School as a postdoc in late 1981 and joined the faculty in 1986.

At Johns Hopkins, Chandrasegaran learned molecular biology at the bench of Hamilton Smith, professor emeritus at the School of Medicine and a key scientific strategist for a private company that published a working draft of the human genome in 2001. Smith shared the 1978 Nobel in physiology or medicine with Hopkins’ Dan Nathans and a Swiss scientist, Werner Arber, for the discovery of restriction enzymes, the first chemical tools for editing DNA.

It was Smith, in fact, who suggested that Chandrasegaran pursue the synthesis for new gene-editing tools. That suggestion eventually led to Chandrasegaran’s groundbreaking work on ZFNs — technology that, Smith notes, “is now leading to discoveries of several new ways to cleave DNA in site-specific fashion without using restriction enzymes. It’s a hot new field with implications for gene therapy and genome engineering.”


Ramalingam, in turn, says Chandrasegaran has inspired him by spending long hours in the lab and generously sharing his skills. “Whenever I end up with some problems, I discuss them with him,” he says. “He’s a great advisor to me.”

—Sivaprakash Ramalingam
On a spring-like Saturday morning in February of last year, Jeanette Walke drove her silver Honda Civic northwest on University Parkway near Johns Hopkins University’s Homewood campus and made a right turn across a bicycle lane into the driveway of her apartment house. Police say she cut off 20-year-old Nathan Krasnopoler—science fiction fan, chess player, enthusiastic amateur cook and Hopkins computer science student—who was carrying a bag of produce home from the Waverly Farmers Market on his Trek bicycle. A police reconstruction of the accident said Krasnopoler swerved, collided with Walke’s car and was thrown in front of it, trapping him underneath. Badly injured and apparently unable to breathe, he was caught between the searing heat of the engine and the pavement. He was still wearing his bike helmet, according to police, but his lungs had collapsed. His broken glasses were found at the scene.

Walke, then 83 years old, climbed out and sat on a low wall as passers-by gathered. A witness told police she held her purse on her lap and seemed to be staring into space until someone asked her to switch off the engine. “I started to turn into the alley, then I heard a crunch like metal crumbling,” Walke later told police investigators. “Then I...
saw a limb like an arm and then I saw a head and I stopped and realized that the person was under my car.” By the time Baltimore firefighters managed to pull Krasnopoler out, he had a broken collarbone, fractured ribs, two collapsed lungs and severe burns to the face. He suffered extensive brain damage from a lack of oxygen and died six months later.

While most media reports emphasized Walke’s age—“Elderly Woman Ticketed in Crash with Hopkins Bicyclist” was a typical headline—Walke told police she was in good overall health. She reported having had glaucoma surgery in 2009 in both eyes, but told police she had visited the ophthalmologist the previous month and was given “a good report.” Walke could not be reached for comment, but her attorney says he did not believe her age played any role in the incident.

Still, the tragic death of Nathan Krasnopoler bore some of the hallmarks of collisions involving older motorists. Walke, who was charged with negligent driving, told police she looked but didn’t see Krasnopoler riding in the bike lane on her right as she approached her driveway. “I kept checking,” she said, according to the police investigation. Experts say that drivers older than 80 or so who are involved in collisions are more likely to report never having seen the other vehicle.

In America and affluent societies around the world, driving has come to be regarded not just as a symbol of youth and independence, but perceived as a basic human right. Giving it up can be hard. If we live long enough, most of us will face increasing mental and physical problems that can affect our ability to drive. Yet many older drivers with declining skills fiercely resist giving up their licenses. Meanwhile some studies suggest that giving up driving can increase social isolation, raise the risk of depression and restrict access to health care—though these problems may be aggravated by other age-related health issues.

Researchers are seeking ways to help keep older people behind the wheel for as long as they can drive safely and to prepare them to call it quits if they can no longer do so. The goal: Help governments, families and society improve road safety while respecting the rights of older citizens.

“Answers, however, have been elusive. “The evidence is really just not there yet on what policies and programs are most effective, and much more needs to be done in the area of older driver research,” says Andrea Gielen, ScD ’89, ScM ’79, director of the Center for Injury Research and Policy (CIRP).

States grappling with the issue have no clear path ahead, says John Kuo, administrator of Maryland’s Motor Vehicle Administration and the governor’s highway safety coordinator. “There’s no norm or best practice that’s surfacing. This is a national dilemma,” says Kuo. “We must develop a strategy that meets their needs and keeps them safely on our roadways.”

Last year saw the first of the baby boomers turning 65. Older Americans are now the fastest-growing segment of the driving population. Today, about one in seven motorists is age 65 or over. By 2025, that figure will be one in four.

In many ways, older people make ideal drivers, says Vanya Jones, PhD ’06, MPH, an assistant professor in Health, Behavior and Society and a CIRP faculty member. “They don’t drink and drive. They wear their seat belts and tend to stay within the speed limit. They do the good stuff,” says Jones who is a passionate advocate for the elderly. The problem, she and other researchers
say, comes when age-related cognitive and physical changes start to affect the complex task of threading a one- or two-ton vehicle through a maze of moving traffic.

Jones is keenly aware of the impact that quitting driving can have on the elderly. She vividly remembers the day her grandfather reached his own painful decision to stop driving. “For me, as a child, he was sort of this larger than life man,” she says. “When he gave up his car, that was one of the few times in his life that I saw him cry.”

Later, while in college in Ohio, she was standing at an intersection when a car hit a pedestrian in front of her. She saw how a life could have been saved if the light had changed a few seconds later or if the driver or pedestrian had slightly altered their behavior. “Personal injuries and motor vehicle crashes are a huge, huge issue for me personally,” she says, saying her concern led to her work with colleagues at CIRP.

Some elderly drivers are as good or better than the average middle-aged motorist. But as we age, researchers say, we experience a gradual erosion of our vision, hearing, response time, mobility, strength and coordination, cognition and judgment. We can also develop a host of age-related illnesses, from glaucoma to diabetes to dementia. To treat what ails us, we may take an array of drugs that separately or in combination can cloud our judgment or slow our reflexes. These changes come sooner for some and later for others, but whenever they come they affect our ability to drive.

“I think there’s often a natural progression as we age,” says Jones, adding that the problem of declining driving skills is “one that we all will probably have to face if we live to be old enough.”

Teenagers and young adults have the worst crash statistics, victims of a cocktail of immaturity and inexperience. But as they spend time behind the wheel, their crash rates go down. Starting around age 75 or so, the process reverses gears, and fatal motor vehicle crashes involving elderly drivers begin to rise sharply. According to the Insurance Institute for Highway Safety, the crash rate per mile for drivers 85 and older is roughly the same as for teenagers. The rate of fatal collisions per mile traveled is close to double that for teens.

Given the physical effects of age, no one is in greater peril in a crash than an older motorist. Someone 80 years of age or older is six times more likely to die in a collision than...
someone 35 to 54 years old. Kuo points out that, nationally, while drivers 65 and over rack up just 8 percent of miles traveled, they account for 17 percent of traffic fatalities. Because of this increased risk of injury-related deaths, Jones says, researchers and traffic safety experts need to find strategies to reduce collisions involving older adults. “You don’t want to be injured in a crash and you don’t want to injure someone else,” she says. “These are really terrifying things.”

The graying of America’s driving population seldom draws much attention until a high-profile tragedy strikes, like the case of George Weller, who in 2003 at age 86 killed 10 and injured 70 when his car barreled through a farmers market in California. In Texas, there were calls for tougher licensing regulations for the elderly after 90-year-old Elizabeth Grimes ran a red light in Dallas in 2006 and slammed into a car driven by 17-year-old student Katie Bolka, who died of her injuries. Likewise, the Krasnopolers case has inspired a call for Maryland to review its policies affecting older drivers.

A recent report by the Trust for America’s Health found that 33 states and Washington, D.C., had some limits for mature drivers, including required vision tests, shorter times between license renewals and limits on online or mailed renewals. That means about a third of states have no such requirements. Some safety activists want to see more restrictive laws on licensing older drivers, including mandatory age-related screening exams or road tests. Following Nathan’s death in 2011, his grieving parents—lawyer Susan Cohen, an assistant attorney general for Maryland at the time, and her husband, engineer Mitchell Krasnopolers—launched a campaign to advocate new licensing rules. In response to public concern, the state Legislature has directed the MVA to conduct a two-year study of older drivers.

According to the Foundation for Traffic Safety at the American Automobile Association (AAA), Maryland requires drivers over age 40 who are renewing their license by mail to submit a report from a vision specialist and requires new drivers over age 70 to provide a medical report. The Krasnopolers want to go further and require drivers, as they age, to take routine cognitive screening exams that may help spot high-risk motorists before they have catastrophic crashes. But state governments are reluctant

**Carl Thistel, 80**

I’ve become more gentle in my driving, not like an old person but like a prudent person. That’s hard; I still have this 17-year-old inside me that likes to get behind the wheel and really see what this sucker will do. I don’t do that anymore.
to demand additional testing for seniors until there is more data showing that these tests work. The Trust for America’s Health, in a May 2012 report, warned against passage of “reactive, unscientific legislation that overly restricts the driving privileges of older drivers.”

The American Association of Retired Persons (AARP) supports tightened testing policies and prelicense screening exams, but not if they’re required based on age. “The only screening method that has been identified that helps reduce crashes among older people is in-person license renewal, and AARP supports in-person renewal across the life span,” says Nancy Thompson, an AARP spokeswoman. “The issue about driving is about health, not age.”

Most older drivers now do what safety experts call “self-regulate,” limiting their driving to match their skills. Edward Ryan, an 89-year-old former engineer at Fort Meade, Maryland, avoids busy streets, the Baltimore Beltway and driving at night. He enjoys short hauls to nearby shopping centers but has no interest in driving on longer trips or in heavy traffic. “I don’t think I miss it, to tell the truth,” he says.

One of Vanya Jones’ chief goals is to find ways to encourage drivers to fine-tune their driving to match their skills and help them prepare to stop driving altogether if the time comes when they are no longer safe on the roads. “We are trying to help adults plan to retire from driving in the same way they would plan to retire from their jobs or change their housing,” she says.

She’s determined, she says, to find an approach to the problem that “honors the individual, that doesn’t disrespect them but also keeps society safe.” And a way to do that, she says, is to find ways to help older adults make their own decisions about driving, including when to stop.

Persuading drivers to take a hard look at their own abilities is not necessarily a straightforward matter.

In a study published in the Journal of Applied Gerontology in December, Jones and a team of researchers from CIRP, the Maryland Highway Safety Office, the Maryland MVA and others administered three standard computer-based cognitive and physical screening exams to 67 older Baltimore County motorists in a laboratory setting. Nine of the drivers, or about 13 percent, were unable to complete or failed two or more of the screening tests and were judged to be at high risk for a crash. (Another 20 were ranked as medium risk because they couldn’t successfully complete one of the screening tests.)

As a group, the nine older drivers judged at high risk had the most trouble with the test that measures the ability to process and sort information.

One of the goals in the study was to see how the high-risk group reacted to being told test results indicated they had a driving-related impairment and should seek medical advice. Jones and her colleagues wanted to learn what participants did with the information, if they would accept the results and seek medical advice or voluntarily stop driving.

From the public health perspective, the results were not encouraging. Of the four drivers who later agreed to in-depth interviews, all said they were uncomfortable with at least one aspect of the testing experience. One told researchers: “Trying to search for a proper word. Disappointed, I guess. Disappointed and [pause] I couldn’t understand why I failed because everybody tells me I’m a good driver.”

Importantly, none of the four who failed the tests disclosed the results to a
physician, and only one surrendered his or her license. The one participant who voluntarily gave up driving said: “I think probably subconsciously it was the reason I gave up my car, because I realized that my reflexes were not as good as they were.”

Despite the small sample, Jones says the study demonstrates how difficult it is to deliver unwelcome news to older drivers in a way that encourages them to act. But she wasn’t surprised, because of the importance of driving to many older people.

When it comes to competency behind the wheel, gerontologists say that chronological age isn’t as important as what is called “functional age.” Steven Gambert, MD, director of Geriatric Medicine at the University of Maryland Medical Center and R Adams Cowley Shock Trauma Center and an authority on the mental and physical effects of aging, recalls testing a former military pilot in his 60s who, as a younger man, had landed a crippled plane armed with a nuclear weapon on the deck of an aircraft carrier. The man’s exceptional skills seemed unaffected by his age. “This guy had superhuman hearing and reflexes,” says Gambert. “He tested off the charts. We couldn’t believe it.”

While many older motorists are highly skilled, Gambert says, others experience a sharp decline starting around age 80. At Shock Trauma, he all too frequently deals with the tragic results.

While Gambert describes himself as an advocate for the elderly, he says that perhaps drivers at a very advanced age, starting in their mid-80s, should be subject to screening that goes beyond an eye test. Drivers with medical conditions or a record of accidents that raises concerns, he says, may need screening earlier. “The reality is, the older you get, probably you’ll get to the point where you’ll need a driver’s assessment,” he says.
Some drivers stay on the road long past the time when they should no longer be behind the wheel. When George W. Rebok, PhD, a professor in Mental Health, was a postdoc studying dementia patients at Hopkins in the 1980s, he discovered that some of his study subjects were driving guided by directions shouted at them by their passengers. Others manipulated the pedals while their spouses steered.

Rebok’s father, Jack Rebok, a retired nuclear power plant engineer, fiercely resisted surrendering his car keys after developing Parkinson’s disease in his early 80s. His family took away his keys, but he had extras hidden around the house. When the family disabled Jack’s beloved Plymouth sedan, a buddy helped him fix it. After Jack Rebok’s doctor reported his declining skills to the state, as required in Pennsylvania, Jack flunked the driver’s test three times and lost his license. But when George saw that his father had visited the barber several miles away, Jack admitted he was driving without a license.

Finally, Jack’s family hid the car and told him it was in the shop for repairs.

While acknowledging such experiences, public health researchers say it is also important to try to keep competent older drivers on the road. Studies have shown that those who stop driving are five times more likely to die within three years. In part, Rebok says, that’s probably because many drivers quit as their health declines. But he also says that the depression, isolation and loss of control that come with giving up driving may—by themselves—cause health problems. In a 2009 study of 690 current and former drivers published in the Journal of Gerontology, Rebok and other researchers found that at the point older motorists quit driving, they reported a sharp, immediate drop in their general health. Quitting also accelerated the physical functioning, social activities and reported a sharp, immediate drop in their overall health. But he also says that probably because many drivers quit as their health declines.

Experts say research is needed into the relationship between giving up driving and household activities, including studies to identify and test coping strategies.

When it comes to cognitive problems, some researchers say new training programs may be able to help older drivers stay safer longer. AARP and AAA offer behind-the-wheel courses designed to help older drivers sharpen their skills. Several commercial firms have produced so-called “brain-training” programs designed to improve driver performance.

In a widely cited study published in Nature in 2010, one team of researchers concluded that thousands of volunteers ages 18 to 60 who played brain-training games online for six weeks did not improve their overall memory or reasoning. Instead, the study found, they improved their skill at taking a particular test.

But Rebok and others believe that an intensive cognitive training program can produce changes that carry over into real life. He is part of a team of researchers participating in a large, long-term, multicenter study called ACTIVE (Advanced Cognitive Training for Independent and Vital Elderly), which in 2006 reported finding evidence that a 10-week program could improve memory, reasoning and speed of mental processing in older adults. In the study of 2,832 volunteers, participants on average reported improvements in their performance of everyday tasks, including driving, that with booster sessions persisted for up to five years after the training ended. The ACTIVE study’s 10-year follow-up was completed last year and the results have not been published, but Rebok says that the training program had a significant impact on cognitive fitness through at least five years.

“I think the results we were getting with the speed of processing in particular shows a lot of promise in terms of extending driver life spans, letting people stay on the road longer and more safely, and shows evidence of actually reducing crashes,” he says. On the other hand, Rebok says, the severely cognitively impaired may reach a point where “there may not be much you can do to bring [them] back to where they can safely operate a motor vehicle.”

A year after Nathan Krasnopoler’s death, the “ghost bike” that his family bought for $30 and painted white still sits chained to a signpost under an elm tree on the sidewalk a few steps from the driveway where he was injured. Walke, now 84, did not respond to a request for an interview, but her lawyer, Robert H. Bouse Jr., says she was deeply affected by Nathan’s death. “It devastated her, it truly did,” he says.

Walke was cited for negligent driving and failing to yield the right of way to a rider in a bike lane, court records show. She pleaded guilty and was fined $220. The Krasnopolars filed a $1 million lawsuit that Walke settled for what the Krasnopolars’ lawyer called a “substantial” sum. The family says they took legal action only after they learned Walke had continued to drive after the accident, and they insisted she surrender her license as part of the settlement.

Now Cohen has left her job with the state Attorney General’s office and plans to use the money from the lawsuit to set up a nonprofit foundation called Safe Roads USA. Cohen says she will dedicate the rest of her life to an effort to promote research, education and legislation to address the problem of older motorists and traffic safety. “I plan to go for laws across this nation,” she says.
a neighborhood cleanup. Regardless of how HIV got into his body, he still had to deal with it. He was nearly driven to suicide by the isolation he felt, but Vinson rallied, thanks in large measure to being invited to a gathering of positive-status youth in Denver by Melody Lynch, an outreach coordinator at Hopkins’ Harriet Lane clinic.

There, Vinson discovered that his status wasn’t a reason to be distraught, that all around him were hundreds of vital young people who could even joke about their status while taking care of themselves. At a talent show there, he read a poem he’d written. It would change his life. The poem, which chronicled his experiences post-diagnosis, won him national recognition and led to a book of poems on lifestyle and HIV titled Positively Me.

Vinson, who was part of the club scene when he first came out, recalls that HIV hung over the crowd like a specter, acknowledged but unspoken. “We were aware, but we didn’t talk about it,” says Vinson, now 22. “And if people were positive, many weren’t going to tell,” and risk being ostracized from having relationships.

Looking back, Vinson says his support system was cobbled together almost serendipitously. There was a relative born with hepatitis C who made sure to get regular liver biopsies, refrained from drinking and told potential partners that he had the infection. “Before he had sex he always told his partners. So if he could handle it, I figured I could.” And there was the older female teacher who, learning of Vinson’s status, said, ‘Baby, I’ve got diabetes. You gotta take care of yourself, I’ve gotta take care of myself, otherwise we’re both gonna die!’”

Now, Vinson has turned his poetry into conversations with concerned youth. His favorite part? Breaking down myths about what the “face” of HIV looks like. In the middle of a PowerPoint presentation, he’ll suddenly turn serious and warn the audience that he’s about to show them what someone with HIV looks like. “I’ll say, ‘Now, if your stomach is weak you should probably leave.’” Then Vinson hits the button, and there’s his handsome, smiling, healthy-looking face, eating an ice cream cone. “Cracks ‘em up every time,” he laughs.

Keith Holt has used his grin to reach at-risk MSM as well. It can be seen on posters for the campaign the 26-year-old helped come up with, “Have Balls, Get Tested,” a Baltimore City Health Department outreach effort aimed at the city’s ballroom community, of which Holt is a part.

To Holt, the idea of a community-gathering spot in Baltimore for young gay African-Americans is a key toward building a safer, healthier community. “When I came out at 17, I realized right then there was no support, no place for me to go. There was Project Olympus, part of HERO [the Health Education Resource Organization, which lost its funding]. I’d like to start something like that again. Some place people know they could come, chill, afterward put on some music and vogue, get to know your peers, and talk about what you’re going through. It’s amazing there’s no place like that here now. You know, the world is coming along in accepting people and their sexuality. I would think the support here would have increased versus decreased.”

For Adrian Ross, activism was triggered by simple observation. “I saw people I was hanging out with all coming up positive. A dear friend became positive, and he never knew until he had full-blown AIDS. It changed my life, and got me out in the community to get people tested,” says Ross. He admits that it was only a few years earlier that he knew nothing about HIV. “They don’t speak of HIV in health classes,” he says of his high school education in Anne Arundel County. “They talk about ways for you not to get people pregnant. It should be mandatory that you take ‘HIV 101’ in high school.”

Ross has found his message is best conveyed through Facebook, where he receives at least two or three messages a week from scared youth seeking education, support and testing information. Ross, who has worked for several Baltimore HIV initiatives, says that many organizations are out of touch with how youth truly interact with social media. “They need to change or they won’t reach who they want to target,” he says. He’s also been shocked to find that some federally funded city HIV-testing programs he’s worked with have turned their back on the MSM community, perhaps looking for other HIV at-risk groups more willing to be tested. “In this city, with this kind of [MSM] work, a lot of people aren’t really dedicated, in my opinion. The last organization I worked at … I was told ‘I’m sick of you targeting the MSM community,’ even though MSMS have the highest risk.”

Taken as a group, these young MSM advocates hit on some common themes: Show commitment. Build trust. Have compassion. Give us professionals who can relate to our world.

It is a message folks such as Danielle German, Karin Tobin, Carl Latkin and Anthony Morgan are hearing loud and clear. By identifying and engaging young, well-connected advocates—think of it as finding the tipping point for MSM at risk for HIV—Karin Tobin says the prevention message can spread organically, from within the community. “We are all embedded within naturally occurring social networks; we are not only influenced by everybody we know, but we are influencing them,” says Tobin. “And so if we can train anybody within this network to educate others, they’re going to influence somebody else; it may well have a broader impact.”