

**stat:** an abbreviation for the Latin *statim*, an adverb that signals a need—for a surgical instrument, a medical supply or, as in this magazine, a short, compelling story—to be met without delay.



JOHN EDER/GETTY IMAGES

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**A DARING DASH** across hot coals creates harmony in the heart-rate pattern of the person striding barefoot and those of friends and relatives watching, suggesting that emotional connectedness can manifest itself physically. During a fire-walking ritual in the Spanish village of San Pedro Manrique, scientists strapped heart-rate monitors to 38 people: 12 about to walk the 23-foot swath of coals, 9 of their friends and relatives, and 17 unrelated spectators. As the walkers made five-second strides across oak embers glowing at 1,251°F, their heart rates synchronized with those of their relatives and friends, but no correlation was found between participants and unrelated spectators.

INTERVIEW //

## When Social Ills Become Medical

■ BY MEERA LEE SETHI

*When pediatrician Nadine Burke opened a clinic for California Pacific Medical Center in San Francisco's Bayview Hunters Point, a neighborhood fraught with gang violence and low-performing schools, she started by offering the usual medical services to a poor population: tetanus vaccines, treatment for asthma and scabies, nutritional counseling to combat obesity. Then Burke read a study that linked "adverse childhood experiences" (ACEs)—including physical or emotional abuse, neglect and having an alcoholic or an imprisoned parent—with an increased risk of heart disease, chronic obstructive pulmonary disease (COPD) and other conditions. Once she dug into the literature, she found a small but compelling body of research that made similar connections. Realizing that the social problems she was seeing were central to her patients' health, Burke began focusing on childhood trauma in her practice.*

**Q: How do ACEs affect health?**

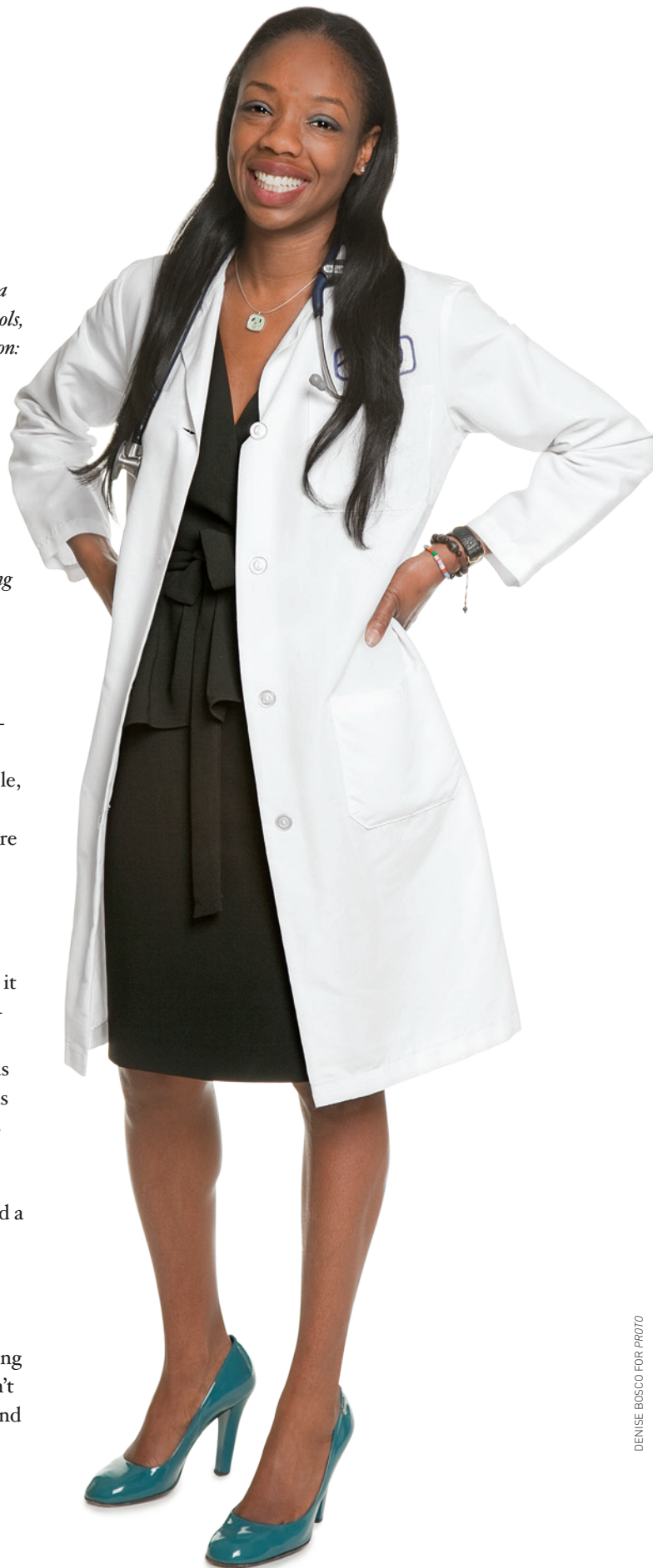
**A:** Repeated trauma causes the body's fight-or-flight mechanism to go out of whack, which affects not only brain function but also the hormone and immune systems. For example, I was trying to figure out what triggered a five-year-old's asthma. Her mom said, "You know, I did notice she had more trouble breathing after her dad punched a hole in the wall."

**Q: And how did your model help you translate that revelation into better care?**

**A:** Before, I didn't have the tools to react to a situation until it reached a crisis point. Then I could have called child protective services or handed Mom a piece of paper with a hotline number—the end. Now I address a patient's social context as a way of practicing preventive medicine. I run weekly rounds where two physicians, two psychologists, two social workers and a clinic coordinator discuss each case. In the example of the five-year-old with asthma, the social worker might propose a home visit and the psychologist might recommend a program teaching parenting skills.

**Q: You've said that what looks like a social situation is often a neurochemical situation.**

**A:** If I see six kids from a school where there's a lot of fighting and they all exhibit learning and behavioral problems, I don't think, "Oh, the kids are just off the hook there." I understand that their environment is affecting them biochemically. We



know that stress and violence raise heart rate, blood pressure and levels of the stress hormone cortisol, and that they affect the immune system by changing helper T cell activity.

**Q: What do you do with that knowledge?**

**A:** I look for interventions that have demonstrated efficacy in reversing those effects. There's wonderful data showing that stress reduction techniques, meditation and biofeedback, for instance, and other supplemental treatments, like child-parent therapy, can decrease heart rate, blood pressure and cortisol levels, and regulate helper T cells.

## ■ “You know, I did notice she had more trouble breathing after her dad punched a hole in the wall.”

**Q: The higher a child's “ACE score,” the greater the health risks, you point out. But isn't childhood trauma more complex than a number?**

**A:** Yes, it is, but whether a patient's relative risk of a disease is 260% or 240%, whether certain types of adversity weigh more heavily than others—that's less important. We can still use this information to guide our management.

**Q: What do high ACE scores mean for your patients?**

**A:** Kids who've been exposed to multiple ACEs have statistically significant increases in obesity and in learning and behavioral problems. The latter is particularly high, and that's not surprising. Studies have linked childhood abuse to

changes in the volume of the hippocampus, which is involved in learning and memory, and stress has been shown to disrupt the balance of neurotransmitters, something that characterizes many behavioral disorders.

**Q: You want all patients, not just yours, to be screened for ACEs.**

**What will help accomplish that?**

**A:** First, perception. Physicians will screen if they know that ACEs are a major risk factor for problems like hepatitis and heart disease—if you have seven or more ACEs, your heart disease risk is higher than if you smoke or have high cholesterol. Second, with

an average of 15 minutes per clinic visit, you're only going to do things you're reimbursed for, so we need a reimbursement structure. Third, say you have a kid with four ACEs. How do you manage him? You know he's at risk for COPD, heart disease and hepatitis, but that's down the line. Do you check liver functions? Cholesterol? We're building the Center for Youth Wellness to figure out best practices.

**Q: Wouldn't some argue that you're overstepping your boundaries as a physician?**

**A:** It is absolutely within my boundaries to evaluate and treat the root cause of disease. If I didn't act, I wouldn't be doing my job. ■

BY THE NUMBERS //

## Sleep, Interrupted

**18 million** Estimated number of Americans who suffer from sleep apnea, a disorder characterized by brief interruptions of breathing that can occur 20 or more times per hour; the combination of intermittent oxygen drops and reduced sleep quality triggers the release of stress hormones, which in turn raise blood pressure and heart rate, boosting the risk of heart attack, stroke and congestive heart failure

**2** Main types: obstructive sleep apnea, the more common, in which relaxation of throat muscles and often a narrow airway leads to pauses in breathing; and central sleep apnea, a rare form in which the brain doesn't send proper signals to the muscles that control breathing

**80** Estimated percentage of people with obstructive sleep apnea who remain undiagnosed

**2** Times more likely that people with sleep apnea suffer from hypertension

**2–7** Times more likely that untreated sleep apnea increases the risk of vehicle crashes

**5** Estimated percentage of weight loss that can help reduce the occurrence of sleep apnea in overweight people, for whom this disorder is more common (fat deposits around the upper airway may obstruct breathing)

**\$150** Low-end cost of one of the most effective treatments: a continuous positive airway device, which holds the airway open by delivering pressurized air through a mask

**30–60** Percent success rate for patients who receive uvulopalatopharyngoplasty surgery to remove excess tissue in the back of the throat ■



INFOGRAPHIC //

## The Genome's Dark Matter

BY BRANDON KEIM //

INFOGRAPHIC BY ROBERT A. DI IESO, JR.

In February 2001, when the human genome's sequence was formally published, the blueprint of human life seemed to be at hand.

But in fact, vast swaths of the genome went undescribed, and there was little sense of how its pieces interacted.

To fill these holes in understanding, the National Human Genome Research Institute launched the Encyclopedia of DNA Elements project, known as ENCODE. Its goal is to find and label every "functional element"

in the human genome and determine how they fit together. The same is being done in modENCODE, the project's model organism counterpart, using fruit flies and roundworms. In December 2010, modENCODE released its first major findings. The human work is expected to follow in the next two years. Here's a sampling of what has been uncovered so far.

### THE ORIGINAL GENOME

Genome mapping is complicated—because it's not physically possible to pull DNA from a cell in one long unbroken sequence, geneticists must extract its chemical components, then reverse-engineer their fit. No surprise, then, that the 2001 genome sequence was very much a work in progress.

#### A CURSORY FIRST PASS AT FINDING PROTEIN-CODING GENES



Analogous to: discovering a few jigsaw puzzle pieces from one corner of a vast puzzle



### THE GENOME IN HIGH RES

In the ENCODE projects, researchers use cutting-edge sequencing technologies to look at everything involved in the genome's operation: each base pair of DNA, piece of RNA, protein, and every last molecule. ModENCODE has already discovered 2,000 previously unknown fruit-fly genes and more than 100,000 new molecules that play unknown roles.

#### SEQUENCING OF GENES AND OTHER "FUNCTIONAL ELEMENTS"



Analogous to: assembling more pieces from throughout the puzzle



### THE ULTIMATE EPIGENOME

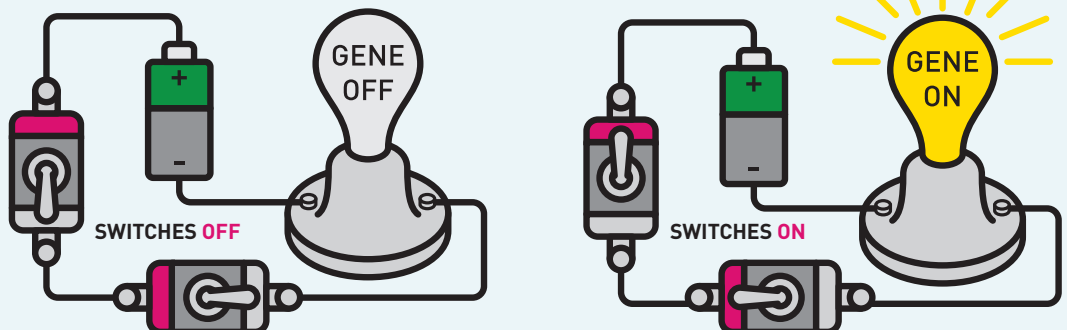
Once genes are identified, the question becomes what happens when they're active or quiet, and what controls the level of activity. This field of study is called epigenetics: Chemical switches form a code overlaid on the genetic one. So far, most attention has focused on just a few of these chemical layers, but the ENCODE projects are analyzing dozens. In the fruit fly, some epigenetic activity seems to be controlled from regions of DNA formerly thought to be inactive.

#### MASTER SWITCHES FOR GENETIC ACTIVITY



Epigenetic activity also occurs in areas once thought of as "junk DNA."

Analogous to: a switch, a power source and a lightbulb



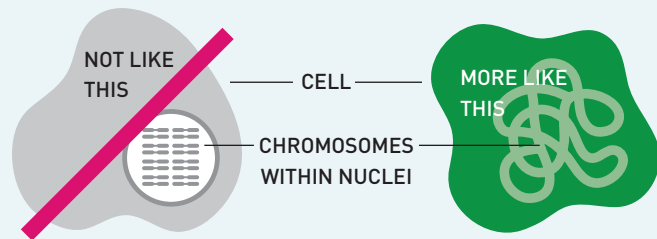


## GENOMIC ARCHITECTURE

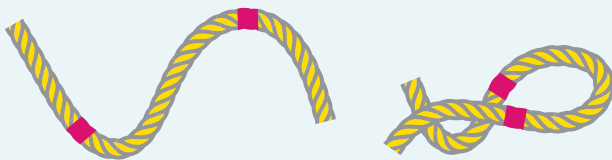
In the popular imagination, genomes are packaged into neatly arranged chromosomes lying flat in a cell nucleus. Chromosomes look that

way before cell division, but otherwise they're tangled in fantastically complex ways, and it appears that gene location in 3-D space affects gene interaction.

### A TANGLE OF CHROMOSOMES



**Analogous to:** marking two points on a rope. Locations that are distant when chromosomes are laid flat may actually be neighbors, sharing proteins and molecules and working in tandem.

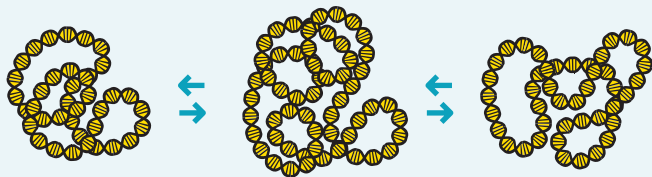


## NETWORK NEWS

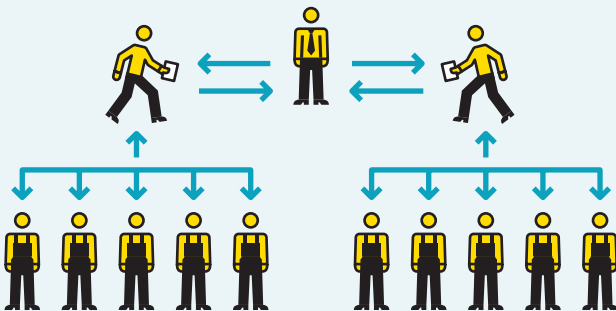
In the past decade, systems biologists have produced maps of gene networks. The results, known conversationally as “hairballs,” flag key clusters of

genes. The ENCODE projects have revealed that hairballs yield hierarchies, with some genes acting as bosses, and others as workers and go-betweens.

### THE HIERARCHY OF GENE INTERACTION



**Analogous to:** orders and feedback being communicated among the boss, middle managers and workers



## MILESTONE //

### The Ethical Investigator



Henry Knowles Beecher wasn't the first to draw attention to research abuses when, 45 years ago, he published a paper in *The New England Journal of Medicine* detailing 22 cases of researchers jeopardizing the health or life of their subjects without informing them of the risks or obtaining their consent. Among the abuses were withholding treatment from soldiers with rheumatic fever and performing extensive, experimental X-rays on newborns. But “Ethics and Clinical Research” was to become a landmark publication, for, as Columbia University medical ethicist David Rothman later wrote, Beecher’s “most important and controversial conclusion” was that such practices “represented the mainstream of science.”

By 1966, Beecher (who changed his name from Unangst to evoke the 19th-century abolitionist Beecher family) had been anaesthetist-in-chief at Massachusetts General Hospital for more than 30 years. A former army physician, he had learned the power of placebo injections in treating soldiers in pain—lessons that Rothman concluded had helped forge Beecher’s belief that randomized, controlled trials were the only antidote to sham therapy.

Beecher’s views on medical ethics, like those of many of his colleagues, were shaped by revelations of Nazi atrocities and the subsequent Nuremberg Code, which insisted on voluntary consent. Yet Beecher believed that the medical establishment had failed to fully absorb the

lessons of Nuremberg at a time when massive increases in government funding were producing an unprecedented expansion of medical research. More money for science meant more subjects to conduct science on—and “science for the sake of science” became a dangerous guiding principle.

Thanks in no small measure to Beecher’s article, medical ethics has shifted radically. International declarations,



institutional review boards and watchdog agencies provide research subjects with more protection than ever.

Still, Beecher, who died in 1976, might not be satisfied. Jay Katz, a Yale University medical ethicist and a friend of Beecher’s, wrote that he felt Beecher’s reliance on the good intentions of researchers was insufficient protection.

In a 1958 paper, Beecher said most breaches of ethical behavior stemmed from “ignorance or thoughtlessness,” not malice. Beecher, Katz wrote, “wanted to teach, not to indict.” Yet that sentiment also underscores why his 1966 vision remains unfulfilled. ■