

# THE INVASION EQUATION

*Will a tumor spread? That may depend as much on your body as on your cancer.*

BY SIDDHARTHA MUKHERJEE

Over the summer of 2011, the water in Lake Michigan turned crystal clear. Shafts of angled light lit the lake bed, like searchlights from a U.F.O.; later, old sunken ships came into view from above. Pleasure was soon replaced by panic: lakes are not supposed to look like swimming pools. When biologists investigated, they found that the turbid swirls of plankton that typically grow in the lake by the million had nearly vanished—consumed gradually, they could only guess, by some ravenous organism.

The likely culprits were mollusks: the zebra mussel and its cousin the quagga mussel. The two species—*Dreissena polymorpha* and *Dreissena bugensis*—are thought to have originated in the estuarine basins of Ukraine, notably that of the Dnieper River. In the late nineteenth century, cargo ships, travelling from the Caspian Sea and the Black Sea, had dumped their ballast water into the Great Lakes, contaminating them with foreign organisms.

At first, the mollusks seemed like relatively innocuous guests. Then things took a turn. By the mid-nineties, they were hanging from ship keels, turbines, and propellers in bulbous, tumorlike masses, encrusting docks and piers, clogging water pipes and sanitation systems, and washing ashore in such numbers that, on some beaches, you could walk on a solid bar of shells. Eventually, the water clarity began to increase, the effect at first picturesque and then eerie.

By 2012, the *Dreissena* population in parts of southern Lake Michigan had reached a density of ten thousand per square metre. By one estimate, there were nine hundred and fifty trillion mussels in the lake, its bottom a crackling carpet of calcium. By 2015, the density was fifteen thousand per square metre—more mussels, by weight, than all the fish in the lakes. Billions of dollars in damage had accumulated. Ships and boats had to be

decontaminated, and water-cleaning equipment dismantled and stripped. Dire warning signs (“DON’T MOVE A MUSSEL!”) were placed throughout the lake system, yet the invaders—the quaggas, ultimately, in the greatest numbers—continued to spread.

What made the mussels such malignant invaders? Some of their aggression is a feature of their biology. The *Dreissena* are champion breeders, each churning out more than a million eggs a year. Yet in the basins and the deltas of Ukraine these mussels seldom reach even a fifth of their peak density in the Great Lakes. They rarely invade depths below thirty metres, clump on boats, clog marine equipment, or form calcified masses. They are, in short, a relatively docile species—restricted, perhaps, by the quality of the water, by their natural predators and pathogens, by the shallowness of the river basin, or by factors we haven’t yet identified.

Solving the quagga conundrum requires cracking two halves of a puzzle. Half the story lies in the mussel’s intrinsic biology—its genes, its morphology, its nutritional preferences, its reproductive habits. The other half involves the match between that biology and the environment. It is a basic insight that an undergraduate ecologist might find familiar: the “invasiveness” of an organism is always a relative concept. The Asian carp—another fierce aggressor in American waters—is not particularly invasive in parts of Asia. The Japanese knotweed, now colonizing the cherished gardens of the English, is hardly known as a weed in Japan. An aggressor in one environment is a placid resident in another. The meek are only circumstantially meek; when conditions change, they might suddenly inherit the earth.

One evening this past June, as I walked along the shore of Lake Michigan in Chicago, I thought about mussels, knotweed, and cancer. Tens of thousands of

people had descended on the city to attend the annual meeting of the American Society of Clinical Oncology, the world’s preeminent conference on cancer. Much of the meeting, I knew, would focus on the intrinsic properties of cancer cells, and on ways of targeting them. Yet those properties might be only part of the picture. We want to know which mollusk we’re dealing with; but we also need to know which lake.

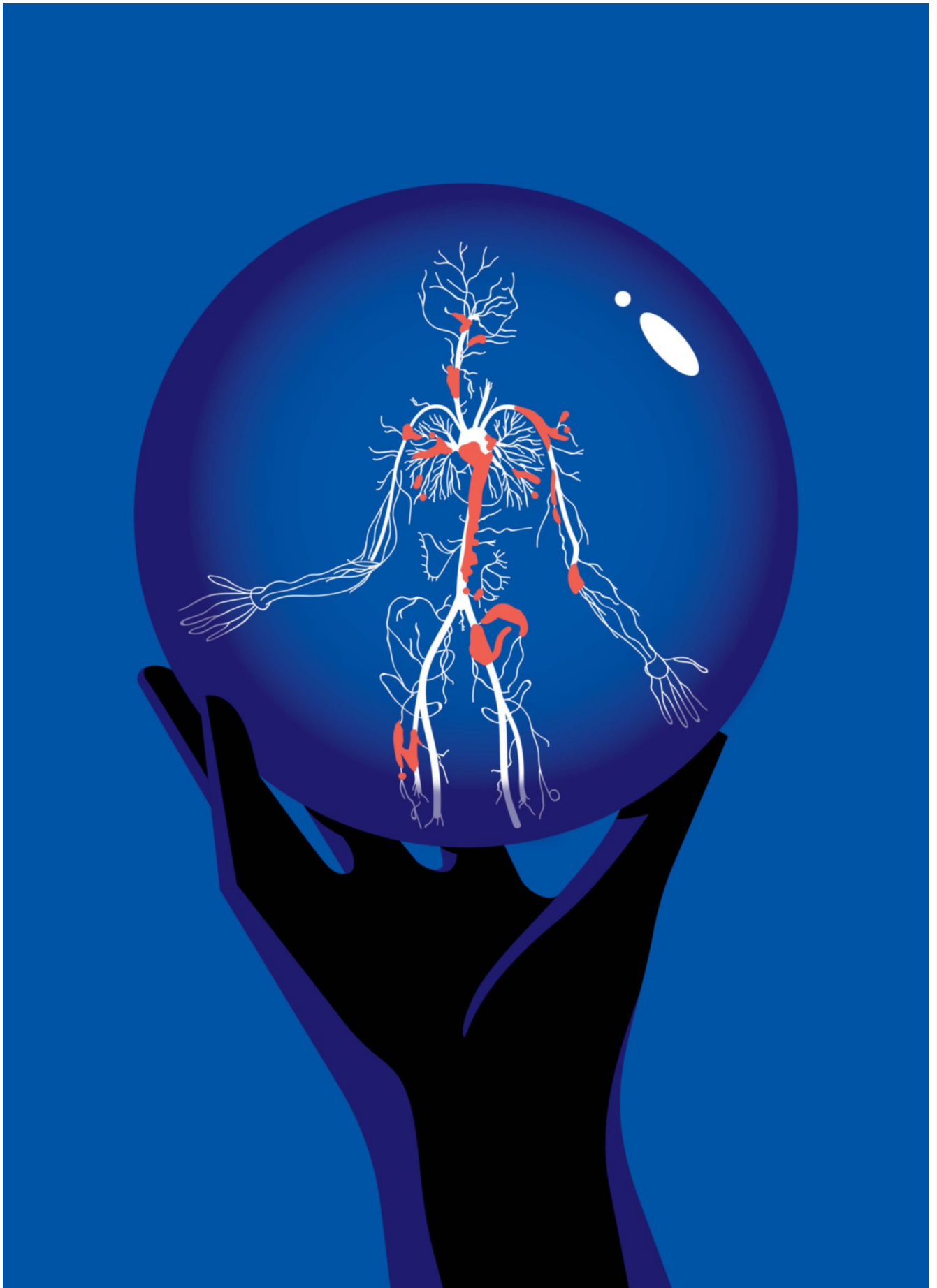
A few weeks before the ASCO meeting, at Columbia University’s hospital on 168th Street, I met a woman with breast cancer. Anna Guzello, a supermarket cashier from Brooklyn, had noticed a small lump in her left breast a few months earlier. (I’ve changed some of her identifying details.) A mammogram then revealed a hazy, spidery mass, and a biopsy confirmed that the tumor was malignant.

Guzello had a total mastectomy of the breast—a simple lumpectomy would not have sufficed, given the size and the location of the mass—and planned to have surgical reconstruction. On an afternoon in May, she came to see Katherine Crew, a breast oncologist at Columbia, to discuss the next steps in her treatment.

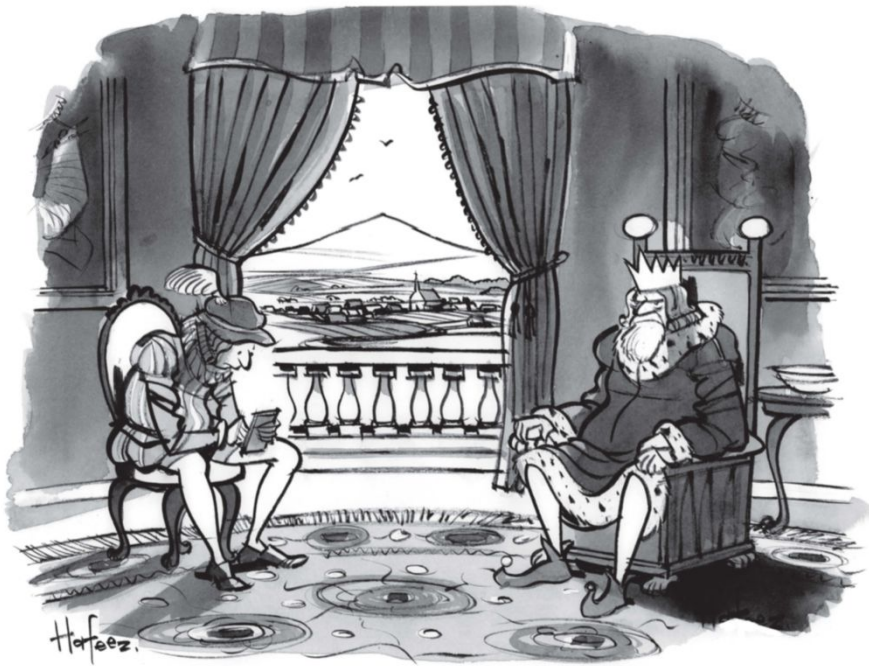
Crew’s office, on the tenth floor of the hospital, is a small, square, sparsely furnished room. The light from a fluorescent desk lamp was flickering, and Crew switched it off. She wanted no distractions. Guzello, her hair coiled into a tight bun, leaned forward, frowning intently, as Crew drew pictures and wrote notes on a sheet of paper.

“Can you read my writing?” Crew asked. “You can keep the notes and always come back with questions.” Her tone was gentle, but it was as if the weight of every word were multiplied.

Guzello nodded. She drummed her fingernails on the table, producing a staccato, military sound—*click-click-click*—a



*We've tended to focus on the cancer, but its host tissue—"soil," rather than "seed"—could help us predict the danger it poses.*



*"The peasants are mercilessly ridiculing you online."*

nervous tic that seemed to calm her.

"First, the good news," Crew said. "There's no visible cancer left in your body."

The surgeons had removed the tumor, with wide margins on all sides. The lymph nodes in the armpits—a frequent site of cancer metastasis—also contained no sign of cancer. In oncology parlance, Guzello would be classified as N.E.D.: "no evidence of disease."

But that's a squirrely phrase: "evidence" refers to the state of our knowledge, not the state of the disease. Breast-cancer cells could have escaped and settled in Guzello's brain, spinal cord, or bones, where they might be invisible to scans and tests. Women with complete mastectomies and "no evidence of disease" can relapse with metastatic breast cancer months, years, or even decades after the removal of the primary cancerous mass. Patients who succumb to cancer generally die of these metastases, not of their primary tumors. (Notable exceptions are brain cancers, which can kill patients by occupying the skull, and blood cancers, in which the cancerous cells are inherently metastatic.)

"So we treat with medicines to decrease the chance of metastasis—the growth of cancer cells in sites outside

the breast," Crew told Guzello. She explained that the medicines came in three main categories: cell-killing chemotherapy; targeted therapies, like Herceptin, that specifically go after the products of misbehaving genes in cancer cells; and estrogen-blocking pills, which are typically prescribed for five or ten years.

Guzello moved her hands over her hair, her lips tightening. The hormonal pills were fine. But she balked at the cell-killing chemotherapy.

"If I don't have those metastases, then I'll be taking risks for no reason," she said. The nails drummed on the table again. The risks were substantial: hair loss, diarrhea, infections, a small possibility of permanent numbness that would leave her hands feeling as if she were wearing leather gloves, yet exquisitely sensitive to cold. The chemotherapy protocol meant that she would be yoked to an I.V. pole at an infusion center for several hours once a week, for nearly half a year. She had a mother with a severe disability to care for, and few vacation days. Was there any way to know whether she was likely to suffer metastasis? "Then I'd be able to assess the risks and benefits more realistically," Guzello said.

The question has echoed through oncology for decades. We aren't particularly

adept at predicting whether a specific patient's cancer will become metastatic or not. Metastasis can seem "like a random act of violence," Daniel Hayes, a breast oncologist at the University of Michigan, told me when we spoke at the ASCO meeting in Chicago. "Because we're not very good at telling whether breast-cancer patients will have metastasis, we tend to treat them with chemotherapy as if they all have potential metastasis." Only some fraction of patients who receive toxic chemotherapy will really benefit from it, but we don't know which fraction. And so, unable to say whether any particular patient will benefit, we have no choice but to over-treat. For women like Guzello, then, the central puzzle is not the perennial "why me." It's "whether me."

There are deep roots to the idea that a cancer's metastases depend on local habitats. In 1889, an English doctor named Stephen Paget set out to understand cancer's "primary growth and the situation of the secondary growths derived from it." The son and nephew of prominent English doctors—his father, James Paget, was one of the founders of modern pathology; his uncle was a Cambridge professor of medicine—the younger Paget might have been burdened by the deadweight of inherited wisdom. Cancer, in Paget's time, was thought to diffuse from its primary site like a malignant inkblot. Surgeons, believing this "centrifugal theory"—cancer's stainlike, outward spread from a central mass—advocated ever-widening surgical extirpations to eliminate cancer. (This theory would form the intellectual basis for William Halsted's "radical" mastectomy.) But when Paget collected the case files of seven hundred and thirty-five women who had died of breast cancer, he found a bizarre pattern of metastatic spread. The metastases didn't appear to spread centrifugally; they appeared in discrete, anatomically distant sites. And the pattern of spread was far from random: cancers had a strange and strong preference for particular organs. Of the three hundred-odd metastases, Paget found two hundred and forty-one in the liver, seventeen in the spleen, and seventy in the lungs. Enormous, empty, uncolonized steppes—

anatomical landmasses untouched by

metastasis—stretched out in between.

Why was the liver so hospitable to metastasis, while the spleen, which had similarities in blood supply, size, and proximity, seemed relatively resistant? As Paget probed deeper, he found that cancerous growth even favored particular sites within organ systems. Bones were a frequent site of metastasis in breast cancer—but not every bone was equally susceptible. “Who has ever seen the bones of the hands or the feet attacked by secondary cancer?” he asked. Paget coined the phrase “seed and soil” to describe the phenomenon. The seed was the cancer cell; the soil was the local ecosystem where it flourished, or failed to. Paget’s study concentrated on patterns of metastasis within a person’s body. The propensity of one organ to become colonized while another was spared seemed to depend on the nature or the location of the organ—on local ecologies. Yet the logic of the seed-and-soil model ultimately raises the question of global ecologies: why does one person’s body have susceptible niches and not another’s?

Paget’s way of framing the issue—metastasis as the result of a pathological relationship between a cancer cell and its environment—lay dormant for more than a century. There were exceptions. The pioneering metastasis researcher Isaiah J. Fidler, working at the National Cancer Institute during the nineteen-seventies and eighties, started to study “cross-talk” between tissue and tumor. A tumor, Fidler showed, is made of a heterogeneous mixture of millions of cells, only a fraction of which are equipped to leave the primary tumor, form an exploitative alliance with the “soil” of another organ, and initiate metastasis. In the same period, Mina Bissell, working at the University of California, Berkeley, and then at the Lawrence Berkeley National Laboratory, began scrutinizing the microenvironments in which tumors formed—or didn’t—as she looked for factors that enabled or disabled the growth of cancer in various organs. Context, she found, was critical.

Yet oncology as a whole remained dominated by a simpler model. When I was a medical student in Boston, I spent an evening in a frigid deli on Boylston Street memorizing the list of bone-metastasizing cancers (breast, lung, thyroid, kidney, prostate) using the unsavory mnemonic “B.L.T.

with kosher pickle” and coming up with a mental image of how metastases might form. Cancer “disseminated” via blood vessels, “attacked” the organs, and began to sprout and flourish there. As I rotated through the cancer wards in the late nineties, doctors reinforced this idea. “This tumor is invading the brain,” one surgeon murmured to another in an operating room. (By contrast, who ever said that the cold catches you?) Subject, verb, object: cancer was the autonomous actor, the aggressor, the mover. The hosts—the patients, their organs—were the hushed audience, the afflicted victims, the passive onlookers.

This language reflected an almost ontological commitment. It persisted even when research paradigms shifted. “Cancer is a genetic disease at its core,” the M.I.T. cancer biologist Robert Weinberg says. For decades, accordingly, biologists have looked for gene mutations that enable some aspect of cancer cells’ aberrant growth, metabolism, regeneration, or behavior. In the late eighties, a number of cancer biologists, Weinberg most prominently among them, threw themselves into finding such genes for metastasis—met genes, in effect. Might a breast-cancer cell, say, acquire a mutation that allowed it to unmoor itself from the breast and colonize the brain?

Despite a decades-long search, the met genes never materialized. “We looked and looked again, but we never found any,” Weinberg told me. Occasionally, mutations were detected in cancer metastases that were different from the primary tumor, but no mutations emerged as singular drivers of metastasis. Starting in the late nineties, cancer geneticists tried another approach. Mutations in cancer cells don’t act in isolation; they can turn dozens, even hundreds, of other genes on and off. And those patterns of activation and repression can make an enormous difference—in the way that similar keyboards can produce wildly different sounds. (A caterpillar has the same genome as the butterfly it turns into, just as your liver cells have the same genome as your brain cells.) Instead of hunting for individual mutations, researchers looked for patterns of gene reg-

ulation—so-called “gene-expression signatures.” These patterns were used to develop predictive tests, which were rapidly shepherd into clinical trials.

For some variants of breast cancer, the tests turned out to be useful. Widely used gene-expression assays, such as MammaPrint and Oncotype DX, have helped doctors identify certain patients who are at low risk for metastatic spread and can safely skip chemotherapy. “We’ve been able to reduce the overuse of chemotherapy in about one-third of all patients in some subtypes of breast cancers,” Daniel Hayes said.

Hayes is also grateful for the kind of genetic tests that indicate which patients might benefit from a targeted therapy like Herceptin (those whose breast cancers produce high levels of the growth-factor receptor protein HER2) or from anti-estrogen medications (those whose tumors have estrogen receptors). But, despite our advances in targeting tumor cells using genetic markers as guides, our efforts to predict whose cancers will become metastatic have advanced only slowly. The “whether me” question haunts the whole field. What the oncologist Harold Burstein calls “the uncertainty box” of chemotherapy has remained stubbornly closed.

In 2001, Joan Massagué, a cancer biologist at New York’s Memorial Sloan Kettering Cancer Center, came upon a scientific paper that radically changed his thinking about metastasis. Originally from Barcelona, Massagué—with his salt-and-pepper hair, his customary button-down shirt with an open collar—resembles a diplomat after embassy hours. He had spent years studying cell biology, elucidating mechanisms of gene regulation that might prime breast cells to travel to the bone instead of to the brain. Then came a crucial piece of evidence, buried in an obscure journal and published nearly three decades earlier. Researchers at the National Institutes of Health had implanted a sac of breast-cancer cells into the ovarian pedicle of a female rat. The cells grew to form a bean-size tumor. The researchers then cannulated a large vein that was draining the tumor and siphoned blood



from the vein every few hours in order to count the number of cancer cells that the tumor was shedding.

The results baffled the investigators. On average, they found, the tumor was sloughing off twenty thousand cancer cells into every millilitre of blood—roughly three million cells per gram of tumor every twenty-four hours. In the course of a day, the tumor molted nearly a tenth of its weight. Later studies, performed with more sophisticated methods and with animal tumors that had arisen more “naturally,” confirmed that tumors continually shed cells into circulation. (The rate of shedding from localized human tumors is harder to study; but available research tends to confirm the general phenomenon.)

“We imagine metastasis as a *going* problem,” Massagué told me. “Mets go to the bone. Mets go to the brain.” He punctuated the air with his fingers at each verb, his face flushed with excitement. “And—yes, yes—*going* is important, because we need to find what allows cells to break away from the tumor and enter the blood and the lymph nodes. But if primary human tumors shed cells continually, and if every cell is capable of forming visible metastasis, then every patient should have countless visible metastatic deposits all over his or her body.” Anna Guzello’s breast tumor should have stippled her brain, bones, and liver with mets. Why, then, did she have no visible evidence of disease anywhere else in her body? The real conundrum wasn’t why metastases occur in some cancer patients but why metastases don’t occur in all of them.

“The only way I could explain the scarcity of metastasis,” Massagué said, “was to imagine that an enormous wave of cellular death or cellular dormancy must restrict metastasis. Either the cells shed by the tumor are killed, or they stop dividing, becoming dormant. When tumor cells enter the circulation, they must perish almost immediately, and in vast numbers. Only a few reach their destination organ, such as the brain or the bone.” Once they do, they face the additional problem of surviving in unfamiliar and possibly hostile terrain. Massagué inferred that those few survivors must lie in a state of dormancy. “A visible, clinical metastasis—the kind that we can detect with CAT scans or MRIs—must only

occur once a dormant cell has been re-activated and begins to divide,” he said. Malignancy wasn’t simply about cells spreading; it was also about *staying*—and flourishing—once they had done so.

In the spring of 2012, while Massagué and others were searching for sleeper cells, Gilbert Welch, an epidemiologist at Dartmouth, was preoccupied with a different problem: the unfulfilled promise of early detection. Early-detection programs aimed to catch and eliminate cancers that were otherwise destined to become metastatic, but a huge ramp-up in screenings for certain cancers hadn’t yielded comparable benefits in the mortality statistics. Welch was trained as a statistician as well as a physician, and when he recites numbers and equations his voice rises to a booming pitch, as if he were a televangelist moonlighting as a math teacher. To illustrate an extreme version of the problem, Welch told me the story of an epidemic—that wasn’t. In South Korea, starting about fifteen years ago, doctors began to screen aggressively for thyroid cancer. Primary-care offices in Seoul were outfitted with small ultrasound devices, and doctors retrained themselves to catch the earliest signs of the disease. When a suspicious-looking nodule was found, it was biopsied. If the pathology report was positive, the patient’s thyroid gland was surgically removed.

The official incidence of thyroid cancer—in particular, a subtype termed



papillary thyroid cancer—began to soar across the nation. By 2014, thyroid-cancer incidence was fifteen times what it was in 1993, making it the most commonly diagnosed cancer in the country. It was as if a “tsunami of thyroid cancer,” in the words of one researcher, had suddenly hit. Billions of Korean wons were poured into treatment; tens of thousands of resected thyroids ended up in surgical buckets. Yet the rate at

which people died from thyroid cancer remained unchanged.

What happened? It wasn’t medical error: observed under the microscope, the questionable nodules met the criteria for thyroid cancer. Rather, what the pathologists were finding wasn’t particularly pathological—these thyroid cancers had little propensity to cause illness. The patients had been not misdiagnosed but overdiagnosed; that is, cancers were identified that would never have produced clinical symptoms.

In 1985, pathologists in Finland assembled a group of a hundred and one men and women who had died of unrelated causes—car accidents or heart attacks, say—and performed autopsies to determine how many harbored papillary thyroid cancer. They cut the thyroid glands into razor-thin sections, as if carving a hock of ham into prosciutto slices, and peered at the sections under a microscope. Astonishingly, they found thyroid cancer in more than a third of the glands inspected. A similar study regarding breast cancer—comparing breast cancer incidentally detectable at autopsy with the lifetime risk of dying of breast cancer—suggests that a hyperzealous early-detection program might overdiagnose breast cancer with startling frequency, leading to needless interventions. Surveying the results of prostate-cancer screening, Welch calculated that thirty to a hundred men would have to undergo unnecessary treatment—typically, surgery or radiation—for every life saved.

“The early detection of breast cancer via mammography saves women’s lives, although the benefit is modest,” Daniel Hayes told me. But equally important is the question of what to do with the tumor we’ve detected: can we learn how to identify those cancers which need to be treated systemically with chemotherapy or other interventions? “It’s not just early detection that we want to achieve,” Hayes went on. “It’s early *prediction*.”

For Welch, the fact that diagnoses of thyroid cancer or prostate cancer could soar without a corresponding effect on mortality rates was a warning: a little knowledge had turned out to be a dangerous thing. Cancer-screening campaigns had expanded the known reservoir of disease without telling us if, in any particular case, treatment was necessary. Early detection helped us with

## SAFE TRAVELS

Every time Gulliver travels  
into another chapter of “Gulliver’s Travels”  
I marvel at how well travelled he is  
despite his incurable gullibility.

I don’t enjoy travelling anymore  
because, for instance,  
I still don’t know the difference  
between a “bloke” and a “chap.”

And I’m embarrassed  
whenever I have to hold out a palm  
of loose coins to a cashier  
as if I were feeding a pigeon in a park.

Like Proust, I see only trouble  
in store if I leave my room,  
which is not lined with cork,  
only sheets of wallpaper

featuring orange flowers  
and little green vines.  
Of course, anytime I want  
I can travel in my imagination

but only as far as Toronto,  
where some graduate students  
with goatees and snoods  
are translating my poems into Canadian.

—Billy Collins

*when* and *what* but not with *whether*.  
And there was an element of mystery.  
Why did some cancers spread and kill  
patients, while many remained docile?

One day in March, 2012, Welch flew to Washington to attend a conference on cancer metastasis. It was a gusty, gray morning—“the hotel was nondescript, the food unremarkable”—and Welch, dangling the requisite nametag on a forlorn lanyard, found himself in a room full of cancer biologists, feeling like an alien species. “I study patterns and trends in cancer in human populations,” he told me. “I take the one-hundred-thousand-foot view of cancer. This meeting was full of metastasis biologists looking at cancer cells under the microscope. I couldn’t tell what any of this had to do with population trends in human cancer—or, for that matter, why I’d even come to this meeting.”

Then, coffee jolting in his hand, he saw a slide on the screen that made him sit up and take notice. It depicted the infestation of mussels in Lake Michigan. The speaker, Kenneth Pienta, an oncologist from the University of Michigan (and now at Johns Hopkins), had heard about the quagga crisis, and been struck by the seeming parallels with cancer. Rather than viewing invasiveness as a quality intrinsic to a cancer, researchers needed to consider invasiveness as a pathological relationship between an organism and an environment. “Together, cancer cells and host cells form an ecosystem,” Pienta reminded the audience. “Initially, the cancer cells are an invasive species to a new niche or environment. Eventually, the cancer-cell-host-cell interactions create a new environment.” Ask not just what the cancer is doing to you, Pienta was saying.

Ask what you are doing to the cancer.

By talking about cancer in ecological terms, Pienta was, in the tradition of Paget and Fidler, urging his colleagues to pay more attention to the soil. A woman with a primary tumor in her breast was caught in a pitched but silent battle. Oncologists had spent generations studying one possible outcome of that battle: when the woman lost, she succumbed to metastasis. But what happened when cancer lost the battle? Perhaps cancer cells tried to invade new niches, but mainly perished en route, as a result of the resistance mounted by her immune system and other physiological challenges; perhaps the select few that, singly or in clusters, survived the expedition ended up languishing in forbidding tissue terrain, like seeds landing on a salt flat.

Welch was captivated. We had to be alert to the differences between the ram-paging quagga mussel and the endangered purple-cat’s-paw mussel—but what about the differences between the Great Lakes and the Dnieper? Evidence suggested, for example, that most men with prostate cancer would never experience metastasis. What made others susceptible? The usual approach, Welch knew, would be to look for markers in their cancer cells—to find patterns of gene activation, say, that made some of them dangerous. And the characteristics of those cells were plainly crucial. Pienta was arguing, though, that this approach was far too narrow. At least part of the answer might lie in the ecological relationship between a cancer and its host—between seed and soil.

**I**n 1992, an Australian high-school teacher in his late fifties was diagnosed with melanoma. The malignancy began as a streak of black—a cancellation sign extending from his left armpit across the torso. A few weeks after the diagnosis, though, the borders of the tumor began to change. One edge turned gray; another shrank. “He had a classic spontaneous regression—typically a sign that the cancerous lesion was being controlled by the immune system,” David Adams, the man’s son, told me. The primary melanoma was surgically resected, and no metastasis was ever found. One of his father’s friends, also in his fifties, was not so lucky: by the time his primary

melanoma had been discovered, his brain was sprinkled with visible mets.

David Adams went on to train as a geneticist and a physiologist in Sydney, before joining the Sanger Institute, in Cambridge, England. There he leads a group studying the biology of melanoma. Originally from Tamworth, a small out-back town in New South Wales (“hot, flat farming country, right in the middle of Australia’s melanoma belt,” he says), Adams now lives ten thousand miles away, in a quaint English village, speaks with a mild Cantabrigian accent, and drives a gently distressed compact car to work. He has, in short, gone native—a matter of soil over seed, you might think—but he hasn’t forgotten his father’s case; it’s what has driven his scientific career. What had made a melanoma regress in one host and turn aggressive in another? Adams knew of a strange series of melanoma cases, occasionally reported in the medical literature, involving donated kidneys. They fit a pattern. A patient—call him D.G.—is diagnosed with a melanoma, and successfully treated with surgical resection.

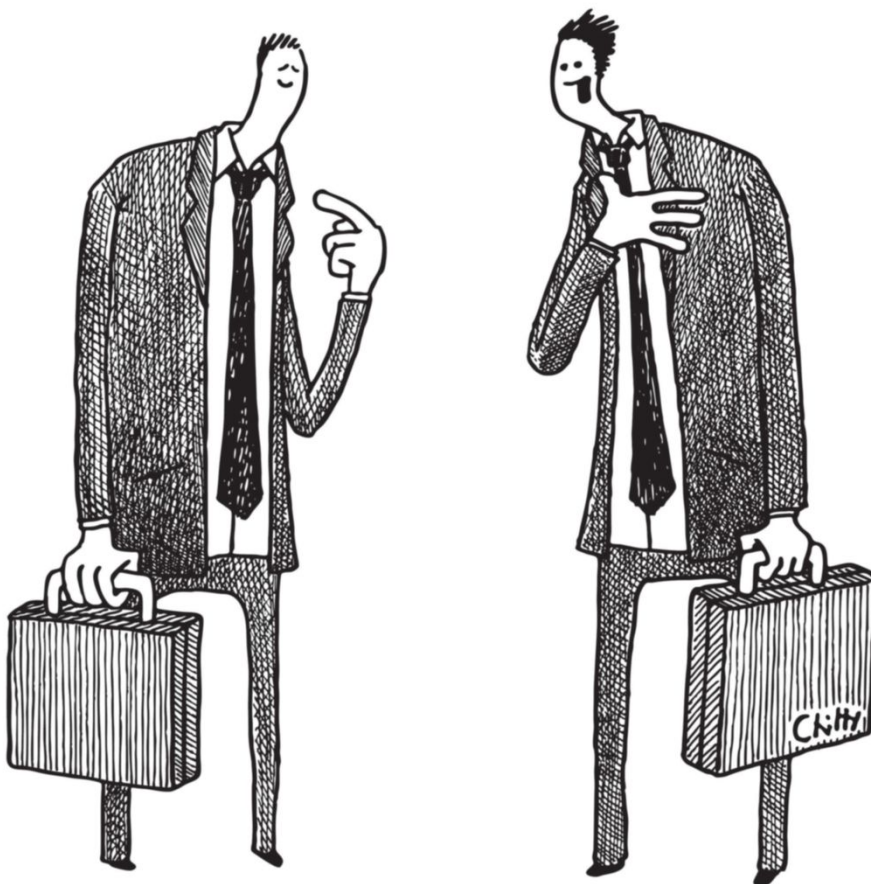
Years later, D.G., now deemed perfectly healthy, donates a kidney to a friend. The friend is prescribed routine immune suppressants to prevent the rejection of the kidney. A few weeks later, however, the recipient begins to sprout hundreds of black pinpricks of melanoma in the kidney. The melanoma, bizarrely, has come from D.G.’s cells. The donated kidney has to be removed. Meanwhile, the donor—like some Dorian Gray of transplantation—remains uncannily healthy, with no sign of melanoma in his body.

Here, too, Adams realized, the original host environment played a crucial role in restricting metastatic growth. The donor’s melanoma cells must have been sitting dormant in the donated kidney, akin to the phenomenon of dormancy that Massagué had found in mice. When the “soil” changed, and the dormant cells arrived in an immune-suppressed recipient, the cancer began to grow. “The immune response in the donor must have been restricting the metastatic cancer’s growth,” Adams told me.

In 2013, Adams began to conceive

an ambitious experiment to identify cancer-suppressing host factors. “Just a few yards from my office, there is an animal vivarium filled with hundreds of genetically altered mouse strains,” he said. “Researchers were using these strains to study the effect of these gene variants on the heart, or on the nervous system. I thought I would ask a somewhat different question: If we implanted these strains with the same cancer, which strains would permit the metastases to grow, and which ones would suppress metastatic outgrowth?”

It was an ingenious inversion of a classic experimental strategy. For decades, biologists have been altering a cancer cell’s genes and injecting the cells into a few standardized strains of mice. The “different cancers into same strain” experiments have allowed cancer biologists to observe how alterations in cancer genes might affect their growth, metabolism, and metastasis. But what effects might variations in the host’s genome have? Adams’s “same cancer into different strains” experiment switched the locus of attention from seed to soil.



*“No kidding—I get up impressively early, too!”*

In New York and Boston, meanwhile, researchers such as Joan Massagué and Robert Weinberg were also investigating “host factors.” In a suggestive experiment, Weinberg and his colleagues studied a cohort of mice whose lungs they had sprayed with thousands of dormant cancer cells. Some mice were exposed to an inflammatory stimulus—the kind that might occur during pneumonia, say—and only in those did the “micro-mets” wake up and turn aggressive. It called to mind a fascinating, if overlooked, experiment that Mina Bissell had done back in the nineteen-eighties. Researchers had known for generations that if you injected a chick’s wing with a certain cancer-causing virus a tumor would grow there. Bissell showed that, when you injected one wing and injured the other, this other wing would grow a tumor, too. On the other hand, if you injected a chick while it was an embryo, there would be no tumor at all. “Back then, it was fashionable to think of cancer only as an oncogene-driven automaton,” Bissell told me. “But here the automaton could be switched on and off by its local environment.” It wasn’t just the seed that mattered; changing features

of the soil could affect whether it would ever germinate.

Massagué and his students were making advances of their own, notably in an experiment in which they depleted various types of immune cells in mice that carried dormant cancer cells. Some of these cell types belong to the “adaptive immune” system, which learns to identify new pathogens and to target them when they next appear. (The adaptive immune system, associated with T cells and B cells, is why vaccines work, and why people seldom get chicken pox more than once.) But the most striking effect occurred when the experimenters depleted another type of cell, the “natural killer,” or NK, cell. These cells belong to our “innate immunity”—they can’t learn anything new but arrive preprogrammed to destroy sick or aberrant host cells. Massagué’s team had implicated these cells as crucial surveyors and controllers of cancer metastasis.

Adams’s particular interest was in host genes, rather than cell types, that might affect metastasis. In early 2013, Louise van der Weyden, a postdoc in Adams’s lab who also happens to be his wife, created a suspension of mouse melanoma cells—a coffee-dark slurry—and injected it into a few dozen mouse strains. Some weeks later, she counted the number of visible mets in the lungs for each strain and rushed the data to Adams’s office.

Even within that small cohort, Adams recalled, the differences were obvious. Some of the mice had developed hundreds of mets—a fusillade of black pinpricks. In still others, the lungs had visibly blackened with metastasis. Yet some mice had developed just a few mets. Adams has a photograph of those mouse lungs above his desk. “Here was the same cancer exerting such different effects in different host environments,” he said.

Two years later, van der Weyden had inoculated eight hundred and ten mouse strains with the melanoma cells and scrutinized the physiology of metastasis in each. Fifteen strains were either moderately or extremely resistant. Twelve of those fifteen strains had gene variations that affected immune regulation, again suggesting the potent role of that system in a cancer’s ability to spread and invade. Even within the resistant group, one mouse strain stood out. Exposed to the dose of cancer cells used in the study,

normal mice developed about two hundred and fifty mets. Mice of this resistant strain, however, developed only fifteen to twenty mets on average. And some of these mice hardly developed any mets at all; their lungs looked pristine and uncolonized even two months after the exposure.

Was this resistance to metastasis peculiar to melanoma, which is a type of cancer well known to provoke an immune response? Adams and van der Weyden tested three other types of cancer: lung, breast, and colon. In all of them, the mouse strain was resistant to the formation of metastases. Notably, the strain carries a variant in a gene called *Spns2*, which, through a cascade of events, increases the concentration of immune cells, notably NK cells, in the lungs—the very cells that Massagué’s lab had identified as a powerful restrictor of metastasis.

David Adams’s father never suffered a recurrence of melanoma; he died from prostate cancer that had spread widely through his body. “Years ago, I would have thought of the melanoma versus the prostate cancer in terms of differences in the inherent metastatic potential of those two cell types,” Adams said. “Good cancer versus bad cancer. Now I think more and more of a different question: Why was my father’s body more receptive to prostate metastasis versus melanoma metastasis?”

There are important consequences of taking soil as well as seed into account. Among the most successful recent innovations in cancer therapeutics is immunotherapy, in which a patient’s own immune system is activated to target cancer cells. Years ago, the pioneer immunologist Jim Allison and his colleagues discovered that cancer cells used special proteins to trigger the brakes in the host’s immune cells, leading to unchecked growth. (To use more appropriate evolutionary language: clones of cancer cells that are capable of blocking host immune attacks are naturally selected and grow.) When drugs stopped certain cancers from exploiting these braking proteins, Allison and his colleagues showed, immune cells would start to attack them.

Such therapies are best thought of as *soil* therapies: rather than killing tumor cells directly, or targeting mutant gene products within tumor cells, they work on the phalanxes of immunological predators that survey tissue environments, and alter the ecology of the host. But soil therapies will go beyond immune factors; a wide variety of environmental features have to be taken into account. The extracellular matrix with which the cancer interacts, the blood vessels that a successful tumor must coax out to feed itself, the nature of a host’s connective-tissue cells—all of these affect the ecology of tissues and thereby the growth of cancers.

Cancers, like mussels, proliferate in congenial habitats, and, like mussels, they can create microenvironments that help them resist predators. Seed therapies kill cells—something like spraying a lake with a mussel poison. Soil therapies, by contrast, change the habitat. When I asked Adams about the kind of clinical trial that excited him because of its therapeutic potential, he discussed an unusual study in which patients who are diagnosed with a primary melanoma—such as his father—will donate blood so that researchers can identify their genetic markers and their immune-cell composition. By studying how they fare over time, we might learn which patient populations are particularly susceptible or resistant to certain cancers. We’d have a better sense of which patients need aggressive treatment. And we might learn something about *how* to treat them—how to alter a susceptible patient’s immunological and histological profile to resemble that of a resistant one.

“Cancer is no more a disease of cells than a traffic jam is a disease of cars,” the British physician and cancer researcher D. W. Smithers wrote in *The Lancet*, in 1962. “A traffic jam is due to a failure of the normal relationship between driven cars and their environment and can occur whether they themselves are running normally or not.” Smithers had overstepped in his provocation. The uproar that ensued was clamorous and immediate; Smithers complained that he had been “lacerated by Occam’s razor.” By arguing that cellular *relationships* were





responsible for cancer's behavior, he had committed the cardinal sin of multiplying the factors that oncologists had to consider. "To deny the importance of cells in tumor growth would be like denying the importance of people in some problem in sociology," he later clarified. Cancer cells were a necessary condition for disease but not a sufficient one. His real aim was to get beyond oncology's obsession with its internal-combustion engine—the cellular automaton and its genes—and only after his death has the field started to come to grips with his message.

**Y**ou ride the subway one morning. The train is delayed at Fifty-ninth Street, and a man in a Yankees cap sneezes on you. At work later that week, you feel the chill entering you quietly, on little cat feet. You take a cab home, now sniffing, cursing the C line and retracing your steps: the culprit with the cap; the empty seat that should have raised suspicion; that slightly moist steel bar you should never have touched. What you do not think about are the six other passengers, sitting nearby, who also got sneezed on. None of them are sick.

This is medicine's "denominator problem." The numerator is you—the person who gets ill. The denominator is everyone at risk, including all the other passengers who were exposed. Numerators are easy to study. Denominators are hard. Numerators come to the doctor's office, congested and miserable. They get blood tests and prescriptions. Denominators go home from the subway station, heat up dinner, and watch "The Strain." The numerator persists. The denominator vanishes.

Why didn't the denominators get sick? The pathogen exposure was the same; the hosts were different. Yet even the term "pathogen" is misleading. A pathogen is defined by its ability to be, well, pathogenic. That's not an inherent attribute, however; it's a relationship, an interaction with the host. Ruslan Medzhitov, an immunobiologist at Yale, has spent much of his life studying host-pathogen interactions. "You can inject the same virus into different hosts and get vastly different responses," he

says. It's the soil that determines the nature of the illness.

And that returns us to the problem with the early-detection paradigm. Suppose we could install tiny sensors in people which would regularly scan their blood to find circulating tumor cells, conducting an ongoing "liquid biopsy." We'd be catching cancers earlier than ever before. But, as with the doctors in Seoul, we might also end up overtreating more cancers than ever before. That's because circulating tumor cells might augur metastatic cancer in some patients, while in others the mets never seem to take hold. Why don't the mets take hold? The old answer was: the cancer wasn't the right kind of guest. The new question is: should we be looking, too, for the right kind of host?

A few months ago, a forty-year-old woman came to my office in a state of panic. She had had a hysterectomy as a treatment for endometriosis. Pathologists, examining her uterus postoperatively, had found a rare, malignant sarcoma lodged in the tissue—a tumor so small that it could not be seen on any of her preoperative scans. She had consulted a gynecologist and a surgeon, both of whom had recommended an aggressive procedure to remove the ovaries and the surrounding tissue—a scorched-earth operation with many long-term consequences. Once these tumors spread, they had reasoned, there's no known treatment. Patients diagnosed with these sarcomas tend to have a sobering prognosis, with most surviving only two to three years after the symptoms appear.

But that's a completely different scenario, I said to her. In her case, the tumor was detected incidentally. There were no symptoms or signs of the cancer. If we sampled ten thousand asymptomatic women, we have no idea how many such malignancies would be found incidentally. And we have no clue how those tumors, the ones found incidentally, behave in real life. Would the alliances formed between the woman's tumor cells and her tissue cells enable widespread metastatic dissemination? Or would these encounters naturally dampen the growth of the tumor and prevent its spread? Nobody

could say. We err toward risk aversion, even at the cost of bodily damage; we don't learn what would happen if we did nothing. It was a classic "denominator" problem, but my response seemed supremely unsatisfactory.

She looked at me as if I were mad. "Would *you* sit and do nothing if someone found this tumor in you?" she asked. She decided to go ahead with the surgery.

Anna Guzello went in the opposite direction, as I recently learned when I checked back with her oncologist, Katherine Crew. Guzello had agreed to take the estrogen-blocker tamoxifen. But she refused chemo, and even Herceptin, despite being HER2-positive. Frustratingly, though, Crew wasn't in a position to say with any confidence what was going to happen.

For decades, our standard explanation for those who make up our "denominators"—i.e., people who meet the criteria of the diagnostic test, who are at risk for a disease, but who may not actually have it—was stochastic: we thought there was a roll-of-the-dice aspect to falling ill. There absolutely is. But what Medzhitov calls "new rules of tissue engagement" may help us understand why so many people who are exposed to a disease don't end up getting it. Medzhitov believes that all our tissues have "established rules by which cells form engagements and alliances with other cells." Physiology is the product of these relationships. So consider our internal-denominator problem. There are tens of trillions of cells in a human body; a large fraction of them are dividing, almost always imperfectly. There's no reason to think there's a supply-side shortage of potential cancer cells, even in perfectly healthy people. Medzhitov's point is that cancer cells produce cancer—they get established and grow—only when they manage to form alliances with normal cells. And there are two sides (at least) to any such relationship.

Once we think of diseases in terms of ecosystems, then, we're obliged to ask why someone *didn't* get sick. Yet ecologists are a frustrating lot, at least if you're a doctor. Part of the seduction of cancer genetics is that it purports to explain the unity and the diversity of cancer in one swoop. For ecologists, by contrast, everything is a relationship among a complex assemblage of factors.



I talked to Anthony Ricciardi, Professor of Invasion Ecology at McGill University, in Montreal. Ricciardi, a biologist, grew up on the banks of Lake Saint-Louis, which bulges out from the St. Lawrence River—the route through which the mussels metastasized to the Great Lakes. “I was familiar with much of what was living in that lake, having played in it as a child and later studied it as a student,” he told me. “And I had never seen a zebra mussel before. Then, one day in June, 1991, while I was working on a research project, I turned over a rock and there was one of them attached to it. It took me a few seconds to recognize what it was. And then I found a few more. That’s when I had a premonition of the invasion to come.”

I asked him why those freshwater mussels went into hyperdrive when they came to our lakes. “You’ve got to understand the dynamics of invasion ecology,” he said. “It’s a series of dice rolls. Most organisms introduced into a new environment will fail, often because they arrive in the wrong place at the wrong time. Vast, vast numbers will die. Piranhas were dumped into the lake for years, but they can’t establish, because the temperature isn’t right for them. People will release marine species like flounder, but the salinity isn’t right for them.” His language, even his tone, was eerily reminiscent of Joan Massagué’s; he might have been describing the waves of cellular death during the establishment of metastasis. “There isn’t one factor but a series of factors that determined how and why the mussels took hold,” he went on.

“But, over all, would you say the temperature of the water was the key?” I asked.

“The water temperature’s a factor. The water chemistry would also have contributed.”

“So a combination of the temperature and the salinity?”

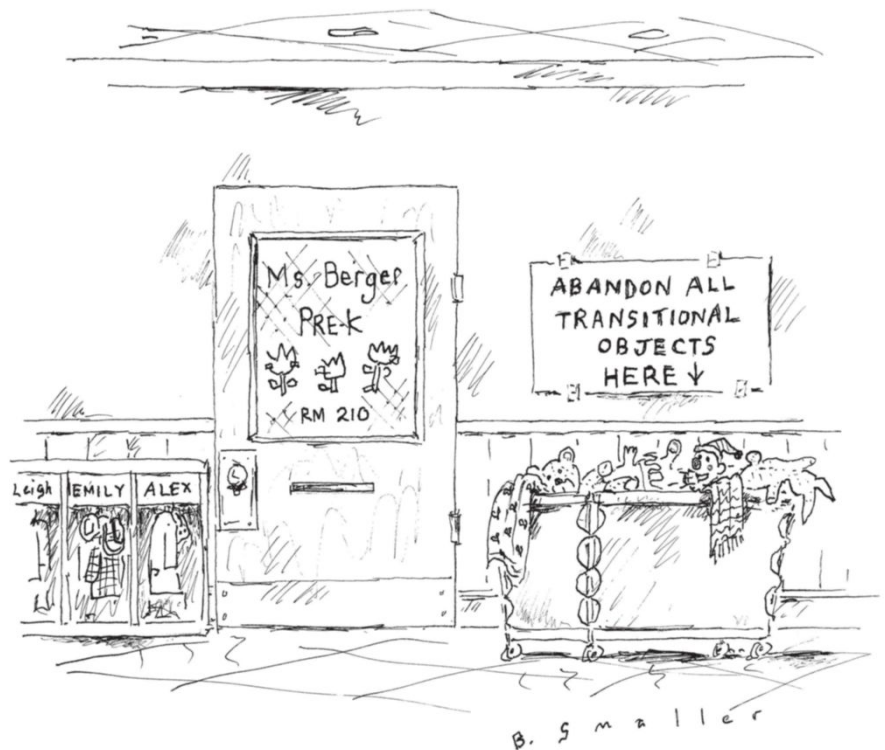
“But also the calcium content. That’s absolutely important.”

I added that to my list of drivers: “Temperature, salinity, calcium . . .”

“And the fact that there weren’t any well-adapted predators. The native fish in these lakes will hardly touch the mussels. Neither will most ducks.”

“Ducks?”

He sighed, as if tasked with explain-



ing an immensely complex theorem to a child. “There are many contributing factors, although some of these factors are clearly more important than others. There are probabilities attached. It’s all context-dependent.”

And so it went. For a cancer geneticist like me, it was an exercise in frustration. Every time I tried to pin down a principal cause for the *Dreissena* invasion, I was presented with another contender. Disheartened, I gave up.

Perhaps we all gave up. Considering the limitations of our knowledge, methods, and resources, our field may have had no choice but to submit to the lacerations of Occam’s razor, at least for a while. It was only natural that many cancer biologists, confronting the sheer complexity of the whole organism, trained their attention exclusively on our “pathogen”: the cancer cell. Investigating metastasis seems more straightforward than investigating non-metastasis; clinically speaking, it’s tough to study those who haven’t fallen ill. And we physicians have been drawn to the toggle-switch model of disease and health: the biopsy was positive; the blood test was negative; the scans find “no evidence of disease.” Good germs, bad germs. Ecologists, meanwhile, talk about webs of nutrition, predation, climate, to-

pography, all subject to complex feedback loops, all context-dependent. To them, invasion is an equation, even a set of simultaneous equations.

Still, at the ASCO meeting this June, on the shore of Lake Michigan, I was struck by the fact that seed-only research was increasingly making room for research that also sifted through soil, even beyond the excitement surrounding immune therapies. Going further and embracing an ecological model would cost us clarity. But over time it might gain us genuine comprehension.

Taking the denominator problem seriously beckons us toward a denominator solution. In the field of oncology, “holistic” has become a patchouli-scented catchall for untested folk remedies: raspberry-leaf tea and juice cleanses. Still, as ambitious cancer researchers study soil as well as seed, one sees the beginnings of a new approach. It would return us to the true meaning of “holistic”: to take the body, the organism, its anatomy, its physiology—this infuriatingly intricate web—as a whole. Such an approach would help us understand the phenomenon in all its vexing diversity; it would help us understand when you have cancer and when cancer has you. It would encourage doctors to ask not just what you *have* but what you are. ♦