MEDICINE AND SOCIETY

How Much Would You Give to Save a Dying Bird? Patient Advocacy and Biomedical Research

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In 1994, Frank McCormack, a pulmonologist interested in innate immunity, arrived at his new job at the University of Cincinnati to find a letter on his desk. It was from Sue Byrnes, a music teacher whose 22-year-old daughter Andrea had been diagnosed with lymphangioleiomyomatosis (LAM), a slowly progressive cystic lung disease that affects about 5 in 1 million women worldwide. Andrea, an avid soccer player, had undergone five operations for a knee injury but remained sidelined. When she began to have intractable abdominal pain, she was told she had irritable bowel syndrome caused by emotional stress. On her seventh visit to the emergency department, she was found to have retroperitoneal bleeding and a 21-cm mass on her kidney — an angiomyolipoma, which the Byrneses later learned was associated with LAM. Chest pain and shortness of breath soon ensued, and Andrea was again told that her symptoms were psychological. Then, during a flight, her lung collapsed. A tension pneumothorax developed, and she arrived at a Denver hospital without a pulse.

Though the doctors in Denver noted cystlike lesions in Andrea's lungs and suspected LAM, her scans were sent elsewhere for confirmation. While they awaited the results, the Byrneses read a research article that suggested that most women with LAM died 5 to 8 years after the diagnosis was made. When they received confirmation of Andrea's diagnosis by mail, they had to tell their daughter themselves what they had learned about the disease. Andrea asked endless questions for which they had no answers. But Sue told her, "I'm going to do something about this. I promise you, I will change all this." Andrea replied, "Mom, you're my best hope."

McCormack, who had been highly recommended by the Denver doctors, knew the therapeutic options for Andrea were limited. He was confronted with the agony of telling a patient, "I'm sorry, but there's not much I can do for you." Having to impart such a hopeless prognosis is sufficiently untenable that many physicians avoid it by offering the patient therapies of unproven benefit.

McCormack took a different approach. He suggested that Sue, who had already begun writing letters to community groups and patients with LAM, enlist pulmonologists around the country to convince the National Institutes of Health to create a LAM registry. Later on, he recommended that she start a foundation, and though he urged her to seek a more renowned pulmonologist to be its scientific director, she refused. "Dr. McCormack had shown heart, compassion, and commitment," she recalls. "That was good enough for me." McCormack and Byrnes have worked together on foundation matters nearly every day since.

In the wake of the 1989 *Exxon Valdez* oil spill, participants in a psychology experiment were asked how much they would pay for nets to save birds from drowning in ponds of crude oil. Three groups were each given the hypothetical opportunity to save a specific number of birds: 2000, 20,000, or 200,000. Despite the differences in the number of birds assigned to each group, the average contributions the participants proposed to rescue them were remarkably similar: $80, $78, and $88, respectively. "What the participants reacted to," writes Daniel Kahneman, "was a prototype — the awful image of a helpless bird drowning, its feathers soaked in thick oil. The almost complete neglect of quantity in such emotional contexts has been confirmed many times."[1]

This psychological disconnect between the impassioned impulse to save a life in danger and the dispassion required when scientific data must be quantified helps clarify the evolving relationship between patient advocacy and biomedical research. Rebecca Dresser, a bioethicist and expert on this topic, recognizes the richness patient advocates bring to clinical research, particularly

in emphasizing outcomes that matter to patients and in identifying patients who are willing to participate in trials. Moreover, advocacy offers an opportunity for purpose and hope in desperate circumstances. But does it offer false hope?

Dresser points to the persistent notion that "all we have to do is throw money at illness and we'll find a cure." There remains a pervasive misunderstanding about the slow pace of clinical research and its frequent failure to deliver. She recalls the actor Christopher Reeve's pleas for funding of embryonic stem-cell research, fostering a mistaken belief that dollars for stem cells would immediately result in paralyzed patients being able to get up out of their wheelchairs.

This impulse to raise money to find a cure, however misguided, has roots in historical triumphs. Around 1948, Sidney Farber was a struggling pathologist seeking to cure childhood leukemia. Thwarted in his attempts to advance testing of his already successful antifolate agents, he had an insight more relevant to human nature than to cell division: cancer needed a poster child (see Part 2 of the documentary video "Getting Better: 200 Years of Medicine," available at http://nejm200.nejm.org/explore/medical-documentary-video/?v=2). Enter Farber's patient "Jimmy," a 12-year-old Boston Braves fan. One night, Jimmy was featured on a nationally broadcast radio show, and as he was quizzed about Braves trivia, the baseball team's players paraded into his hospital room. Listeners were told that if $20,000 were donated, Jimmy would get a television to watch the Braves play. Thus was born the Jimmy Fund, which not only has raised more than $750 million to date, but also established what remains a unifying principle of advocacy efforts: in order to generate funding and awareness, every disease must have a face.

In 1992, my aunt, a 41-year-old attorney and compassionate spitfire, elected to undergo high-dose chemotherapy with autologous bone marrow transplantation (HDC-ABMT) — a last-ditch measure for treating her widely metastatic breast cancer. HDC-ABMT was an experimental therapy that had been tested with modest success in phase 2 trials. Phase 3 testing hadn't been completed, but because HDC-ABMT constituted a more intense version of a treatment already approved by the Food and Drug Administration (FDA), it fell outside the purview of the usual approval process. My aunt had three young children, and HDC-ABMT seemed to be her only hope.

By then, AIDS activism had changed the very nature of patient advocacy. Physicians' willingness to prescribe HDC-ABMT off label permitted its decade-long use. But patient advocates were profoundly influential in making the investigational treatment accessible and appealing. As Siddhartha Mukherjee explains, "AIDS activism had transformed" the idea that experimental treatment was appropriately "unavailable for general public use."[2] Activists insisted that an investigational agent was not "a hothouse flower meant to be cultivated only in the rarefied greenhouses of academic medicine, but rather a public resource merely waiting in the warming antechamber of science while doctors finished clinical trials that would, in the end, prove the efficacy of said drugs or procedures anyway."[2]

In the case of AIDS, militant activism proved lifesaving. Progress in treating patients with HIV infection and AIDS depended as much on impassioned advocacy as on understanding retroviruses (see Part 3 of the documentary video "Getting Better: 200 Years of Medicine," available at http://nejm200.nejm.org/explore/medical-documentary-video/?v=3). When men were dying in agonizing and unprecedented ways, unable to obtain drugs that showed promise in clinical trials, protestors demanded that approval of antiretroviral therapy be expedited. As famously noted by Larry Kramer, founder of the AIDS Coalition to Unleash Power (ACT UP), "Double-blind studies were not created with terminal illness in mind."[2]

By 1992, regulatory burdens were relaxed, and the FDA initiated the Accelerated Approval Program, allowing drugs for life-threatening and otherwise untreatable diseases to be approved on the basis of surrogate end points. Thousands of patients who would otherwise have died began receiving effective treatment.

Although such leniency was a coup for AIDS activists, the same impulse backfired in the case of HDC-ABMT, in which patient advocates focused on insurers that refused to cover this experimental therapy. The advocates urged women to take their cause to the courts. Stories of young women dying at the hands of faceless, profit-driven insurance companies were captivating, and the impulse to "save the dying bird" often

prevailed. In one case, a federal judge noted, "To require that the plaintiff or other plan members wait until somebody chooses to present statistical proof . . . that would satisfy all the experts means that plan members would be doomed to receive medical procedures that are not state of the art."[3] Hamstrung, insurers agreed to cover the cost of HDC-ABMT, which averaged around $80,000. As a result, over the course of a decade, some 41,000 women opted to undergo the therapy, with about 9 out of 10 women choosing to receive the treatment outside a clinical trial.[4]

After undergoing HDC-ABMT, my aunt spent 41 days in the hospital, wracked by infection and misery, and then died. The treatment was covered by her insurers but probably shouldn't have been. After years of painfully slow trial enrollment, investigators finally reached some scientific truth: Among women with metastatic breast cancer, HDC-ABMT causes more harm than good.[5]

People tend to magnify the risks posed by emotionally salient events and to underestimate the risks posed by more common events — part of a phenomenon called the "availability cascade." For example, although the risk of dying of asthma is nearly 20 times that of dying in a tornado, people consistently believe that tornadoes are the more likely killers.[1,6] The cascade occurs when the media latch onto an emotionally charged event and ignite the public imagination so that not only the event but the fact that people care about it becomes a story — and a political issue.

Consider the withdrawal of approval of Avastin (bevacizumab) for women with end-stage breast cancer or the outcry against the recommendation by the U.S. Preventive Services Task Force that mammography screening for women under 50 years of age be done less frequently. The mind sees the faces of women who insist that Avastin or mammography saved their lives rather than the countless others who were harmed by these interventions. I believe that the same cycle of emotional availability and media coverage trapped insurers into paying for HDC-ABMT for women with metastatic breast cancer.

The challenge inherent in the evolving relationship between patient advocates and biomedical research lies in this psychological netherworld where emotions and numbers intersect. It is the advocate's job to give a disease emotional salience, to put a face to the illness and make people care. But it's the physician-scientist's job to generate data, analyze the data to permit reasoned risk–benefit assessments, and communicate those judgments to the public. Both roles are critical, but what happens when they merge? As Dresser notes, "Patient advocacy organizations that once let scientists determine the research agenda now decide for themselves what leads are most promising and award funds to researchers willing to pursue those leads. . . . A new breed of patient advocate sits at the table with scientists and policymakers, setting research agendas, planning studies, and considering how study results should affect clinical practice."[7]

The newest stage of this evolution is apparent in the Patient-Centered Outcomes Research Institute (PCORI), which will oversee comparative-effectiveness research. As Ellen Sigal, a patient advocate and PCORI board member, notes, patients have long been "symbolically at the table" but "only in a check-the-box sort of way." PCORI's very mission is to fund research that matters to patients. Says Sigal, "The information that patients value may differ from the information that trials typically seek. Patients can remind researchers of the importance of quality of life or side effects of chemotherapy. Patients can also remind researchers, 'I would never enroll in a trial like that.'"

But what kinds of trials should patients enroll in? Here, the ethical challenge of trial design can collide with the passions of advocates — with unknown consequences. Sigal's organization, Friends of Cancer Research, for instance, recently worked with Congress and the FDA to add a clause to drug regulations allowing certain drugs that show promise in phase 1 testing to be granted a "breakthrough" designation. Drug sponsors would collaborate with the FDA early on, aiming to shorten the time to approval and minimize the number of patients assigned to receive comparatively ineffective control regimens.

Vemurafenib, for example, a BRAF inhibitor recently approved for treating melanoma, showed tremendous promise in phase 1 and phase 2 trials, but this drug consequently created profound distress during phase 3 testing when some patients who could clearly benefit were instead receiving

a control drug known to be ineffective. Was continued ineffective treatment really necessary when a new therapy was producing responses in 50% of patients?

But controls exist for a reason. Will the breakthrough designation foster successful scientific advances, as with AIDS, or tragically uncontrolled experimentation, as with HDC-ABMT? Of course we should pay attention to what matters to patients. But robust clinical trials must continue. As Dresser emphasizes, "Research is not treatment."

Sue Byrnes has never conflated the two. Research remains the LAM Foundation's core mission, though patients remain critically involved in the process. During an annual meeting, researchers share their insights into the disease with patients, who in turn offer testimonials about living with LAM. This model, says McCormack, has fostered a collaborative, informed spirit that has driven progress against LAM.

Indeed, since Byrnes began her efforts, the research environment and treatment paradigm for LAM have been transformed. In 1994, there was no LAM registry; today, the LAM Foundation has identified 1800 patients throughout several countries. Funding for LAM research, which was nonexistent at the time of Andrea's diagnosis, surpassed $40 million from federal and other sources, plus more than $10 million from the LAM Foundation, in 2011. Most important, young women with LAM need no longer be told that nothing can be done about their disease. Last year, McCormack and colleagues published the results of the first randomized, controlled trial for LAM, which showed the efficacy of sirolimus in preserving pulmonary function and improving quality of life.[8]

McCormack acknowledges that the trial would have been impossible without the 15 years of research preceding it, plus some serendipity: one fortuitous event was the finding that the genes that cause tuberous sclerosis also encode a protein, the deficiency of which activates the cell-growth pathway in the lungs of patients with LAM. Coincidentally, sirolimus, which specifically targets that pathway, had just been approved by the FDA. But most critical was that impulse to save the metaphorical drowning bird.

As McCormack notes, "What LAM has taught me about medicine and health systems pales in comparison to what LAM has taught me about human nature." He emphasizes physicians' tremendous volunteerism: "I can't recall a single physician investigator we called who said no. They are primarily motivated by wanting to have something to offer their patient."

And as pointed out by Alan Barker, a pulmonologist at Oregon Health and Science University and an investigator in the sirolimus trial, physicians' altruistic impulse was matched by that of patients: "The women who participated in the trial made enormous sacrifices. They travelled great distances. They were given no guarantees on anything."

"Put yourself in their shoes," McCormack says. "Half of normal lung function remaining, declining by 10% year after year, and signing up with the 50% chance that lung function would drop by another 20% on placebo while the promising drug being tested is available with a prescription from any doctor and a trip to the pharmacy." But hearing these numbers did not temper the patients' desire to help; they knew their participation remained essential to the scientific process.

We are thus left with a paradox: although the altruistic impulse may make our minds less receptive to data, it is this very impulse that allows us to generate data in the first place. But if emotional responses are insensitive to numbers, numbers are equally insensitive to the human psyche. Establishing any drug's safety and efficacy depends on an acceptable benefit–risk ratio, but the values assigned to the variables that we include in those ratios will always be a matter of debate. How can we quantify the agony of facing an untreatable disease? Can we measure the harms we inflict because we can't bear to tell patients they have no options? Can we assign a numerical value to hope? For those aspects of disease that elude our measurement, we will forever depend on the insights and passions of our patients.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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