

PERSPECTIVE

Unanticipated Outcomes: A Medical Memoir— A Book Review

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Unanticipated Outcomes: A Medical Memoir is the story of Jerome P. Kassirer, MD, MPH, who was born at the height of the Great Depression, grew up in a “two story-rat infested wooden house”^{1(p16)} in Buffalo, New York, and, in 1991, became the sixth Editor in Chief of the *New England Journal of Medicine (NEJM)*. Kassirer’s memoir¹ takes us through the life of a legendary figure in modern medicine, a man who, above all else, embodied what it meant to be, and, what it still means to be, a professional. At a time when we increasingly read about disillusionment and burnout among physicians, the high costs of drugs and care, and the corrupting influences of money on medicine, Kassirer’s book¹ reminds us why we became doctors. His life lessons are timeless.

Growing up, Kassirer worked his way through school washing windows, selling shoes, and driving a bakery truck. Despite receiving a college scholarship, the only college he could attend was the University of Buffalo because he could only afford to live at home. Although he was at the top of his class in medical school, also at the University of Buffalo, Kassirer was rejected from every Boston internship program that he applied to. Instead, he completed his internship in Buffalo, and was on track to spend his life in that city, when he made a diagnosis—during his first week of internship.

The patient was a 58-year-old woman with a 2-year history of fatigue, chronic diarrhea, hot flashes, weight loss, an enlarged liver, and episodes of sudden drops in blood pressure. Kassirer confidently wrote “carcinoid syndrome” in her chart. His diagnosis was correct, and the case was published,² earning him acclaim, and later a fellowship in Boston. But his reflection, years later, tells us more. Kassirer writes, “Had I known then what I know now about disease incidence and prevalence, namely that rare diseases are rare and any positive test for it is most likely to be a false-positive result, I doubt I would have been so certain.”^{1(p24)}

Diagnostic reasoning was on Kassirer’s mind as he worked his way from nephrology fellow to professor of medicine at Tufts University School of Medicine. As late as the 1970s, the primary method by which doctors were taught to reach diagnoses was through Venn diagrams. In this method, a doctor listed findings from a patient’s medical history, as well as physical and laboratory tests. Venn diagram circles for diseases were applied to explain the findings, and the most parsimonious diagnosis or set of diagnoses was pursued. The method had powerful proponents, such as Alvan Feinstein, MD, a famed professor at Yale. Yet, in 1975, Kassirer and the cardiologist Steve Pauker, MD, proposed an alternative—a Bayesian approach to decision making.³ Bayesian decision making meant considering the pretest probability that a diagnoses was possible and used clinical tests to

refine that probability.⁴ It is largely the method taught today. Kassirer’s story reminds us that advances in medicine may challenge or threaten the views of powerful figures.

Kassirer’s pioneering work in clinical decision making is likely one of several factors that led to his selection as the Editor-in-Chief of the *NEJM*. In the journal *Hospital Practice*, which was distributed freely to a wide audience of physicians, Kassirer and Rick Kopelman, MD, had published 78 consecutive monthly installments of “Clinical Problem Solving,” and soon after Kassirer became Editor-in-Chief, he brought this feature to the *NEJM*. In contrast with prior case reports that presented a meticulously worked-up case from the outset, a clinical problem solving case provides the information piecemeal, as a physician would receive it. The format forces the discussant to explain her or his thinking and how this thinking changes as more information emerges. The *NEJM* continues to publish these cases, and many clinicians have honed their diagnostic acumen by reading them.

Unanticipated Outcomes: A Medical Memoir includes many highlights from Kassirer’s tenure at the *NEJM* from 1991 until 1999; 2 are particularly informative.

First, in 1994, the *NEJM* learned of data errors in the National Surgical Adjuvant Breast and Bowel Project (NSABP). Trials from this project, known as Protocols B-06, B-13, and B-14, which are the foundation of breast oncology, justifying lumpectomy and radiation therapy as an alternative to mastectomy, adjuvant chemotherapy, and hormonal therapy.⁵ At 1 of 484 study sites, an investigator falsified patient records. Bernard Fisher, MD, the principal investigator of the NSABP, provided assurances that, the overall study results stood. Such assurances, however, were not enough. The *NEJM* under Kassirer, “insisted on receiving fully audited and corrected data and taking the paper again through the journal’s peer review process.”^{1(p97)}

Contrast this requirement to the approach to the ROCKET-AF trial, published in the *NEJM* in 2011.⁶ This industry-sponsored trial found that in patients with non-valvular atrial fibrillation rivaroxaban was noninferior to warfarin for the prevention of stroke or systemic embolism.⁶ In 2014, the US Food and Drug Administration recalled the device used to measure the international normalized ratio in the warfarin arm.⁷ Although there were calls for an external review,⁷ the *NEJM* did not demand an independent audit. Instead, it took the investigators word that the results remained valid.⁸

Second, Kassirer took financial conflicts of interest very seriously. Under his tenure, the *NEJM* did not allow opinion articles (mostly editorials) or review ar-

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ticles to be written by authors with financial ties to the products discussed or their products' competitors.¹ A wealth of empirical data justifies this position.⁹ After Kassirer's departure, the *NEJM*'s weakened this restriction on authors. Kassirer thought the new policy was misguided and said so publicly.¹

Both of these anecdotes capture a broader trend for medical journals to increasingly accommodate their authors. Kassirer understood that the primary responsibility of a journal was to its readers and that a preeminent journal such as the *NEJM* was in a unique position to assure that the conduct of the authors served the interest of its readers. In 2017, nowhere is this lesson needed more than in ensuring data sharing from clinical trials, a proposal that the International Committee of Medical Journal Editors recently backed down from.¹⁰

The epigraph for *Unanticipated Outcomes: A Medical Memoir* is, "He should have seen it coming." No doubt the epigraph refers to the firing of Kassirer in 1999 after 8 years of a highly successful tenure. Kassirer had persistent and rancorous clashes with the Massachusetts Medical Society and the owner and publisher of the *NEJM* regarding use of the *NEJM* brand to legitimize other commercial ventures. Kassirer felt strongly that the reputation of the *NEJM* was too

important to be sold away and vigorously opposed such efforts. His unwavering opposition earned the scorn of the leadership of the society and eventually led to his dismissal. In his book,¹ Kassirer makes the case that perhaps he should have seen his dismissal coming. But had he known, one wonders, if he would have done anything differently.

Kassirer tried to improve how physicians think and practice. Although he won many battles, he lost others. Once, after writing an editorial on the danger of gun ownership, a senior official at the Centers for Disease Control and Prevention asked him not to be too vocal about the epidemiology of gun injuries. Kassirer thought the warning was absurd—"the more noise the better."^{1(p86)} The warning however was apt, and Congress later cut funding for the National Center for Injury Prevention and Control. Kassirer had, "underestimated the strength of the gun lobby... [and] overestimated the power of facts and logic."^{1(p86)}

After reading this spellbinding, rich, and wonderful memoir, one cannot help but wish that there were more in medicine who would be willing to underestimate the powerful groups that benefit from the status quo and overestimate the ability for facts and logic to prevail.

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