A note about the notes: What follows is a small fraction of the references relevant to each of the issues discussed; when applicable, I've focused on papers published by our group in DoPE, using links that are publicly available whenever possible. Readers who work at a university or academic medical center will have ready access to journal articles through the citations provided. For others, federally funded projects are required to provide public access through the government's PubMed Central; when that's the case, clicking on the PMC "Free Content" box should send you there. A companion website, RethinkMeds.info, will provide active hyperlinks for all citations that have them, along with updates and corrections that are likely to be necessary in a book that takes on as many issues as this one does.

INTRODUCTION: A FRIEND OF THE COURT

- 2 *the doctor who prescribed it*: Increasingly, prescriptions are also written by nurses, pharmacists, physician assistants, and other health-care professionals. The latter phrase is cumbersome, and the term "provider" is unpleasant. The use of "doctor" in the text should be seen as including these other colleagues as well.
- 3 my last book: Jerry Avorn, Powerful Medicines: The Benefits, Risk, and Costs of Prescription Drugs (New York: Knopf, 2004).
- 9 book on the 1968 student movement at Columbia: Jerry Avorn et al., *Up Against the Ivy Wall: A History of the Columbia Crisis* (New York: Atheneum, 1968). It is available on Amazom.com and for free at the Internet Archive: https://archive.org/details/upagainstivywall00avor.
- 10 Some of the most important questions we've tackled: For example, I saw that older patients given antipsychotic medication to manage their behavior were sometimes brought in by family members to evaluate their "new Parkinson's disease." Our group was able to show that this is a common and often misdiagnosed side effect of those drugs: J. Avorn et al., "Neuroleptic Drug Exposure and Treatment of Parkinsonism in the Elderly: A Case-Control Study," American Journal of Medicine 99, no. 1 (July 1995): 48–54, doi: 10.1016/s0002-9343(99)80104-1, PMID: 7598142, https://pubmed.ncbi.nlm.nih.gov/7598142/.
- 10 the Division of Pharmacoepidemiology and Pharmacoeconomics: See www.Drug Epi.org for an overview of DoPE's work.
- 10 harvest such data on a very large scale: S. Schneeweiss and J. Avorn, "A Review of Uses of Health Care Utilization Databases for Epidemiologic Research on Ther-

- apeutics," *Journal of Clinical Epidemiology* 58, no. 4 (April 2005): 323–37, doi: 10.1016/j.jclinepi.2004.10.012, PMID: 15862718, https://pubmed.ncbi.nlm.nih.gov/15862718/.
- 11 among the most highly cited researchers in the country: Jerry Avorn: https://www.adscientificindex.com/scientist/jerry-avorn/4512570; Aaron Kesselheim: https://www.adscientificindex.com/scientist/aaron-kesselheim/4511833; Sebastian Schneeweiss: https://www.adscientificindex.com/scientist/sebastian-schneeweiss/1388992.
- 11 spin-off nonprofit organization: Alosa Health, www.AlosaHealth.org.

CHAPTER 1: HOW DO WE KNOW?

- 21 book about the Soviet Union: Peter Pomerantsev, This Is Not Propaganda: Adventures in the War against Reality (New York: Public Affairs, 2019).
- 22 "Americanitis Elixir": Greg Daugherty, "A Brief History of 'Americanitis," Smithsonian, March 25, 2015, https://www.smithsonianmag.com/history/brief-history-americanitis-180954739/.
- 23 attempt at drug regulation: The most comprehensive history of the FDA's development is Daniel Carpenter, Reputation and Power: Organizational Image and Pharmaceutical Regulation at the FDA (Princeton, NJ: Princeton University Press, 2010). Another account is Philip J. Hilts, Protecting America's Health: The FDA, Business, and One Hundred Years of Regulation (New York: Knopf, 2003).
- 24 medication effectiveness: In optimal usage, "efficacy" describes how well a drug works in the formal setting of a randomized controlled trial, while "effectiveness" describes how well it performs in routine use. However, these terms are often used interchangeably—a problem made worse by the fact that much of the FDA's enabling legislation uses "effectiveness" when it means "efficacy."
- 28 over a thousand furious AIDS protesters: "Seize Control of the FDA," ACT UP Oral History Project, https://www.actuporalhistory.org/actions/seize-control-of-the-fda.
- 30 Accelerated Approval: J. J. Darrow, J. Avorn, and A. S. Kesselheim, "FDA Approval and Regulation of Pharmaceuticals, 1983–2018," *JAMA* 323, no. 2 (2020): 164–76, doi: 10.1001/jama.2019.20288, https://jamanetwork.com/journals/jama/article-abstract/2758605.
- 31 surrogate measure-accelerated approval system: M. Mitra-Majumdar et al., "Analysis of Supportive Evidence for US Food and Drug Administration Approvals of Novel Drugs in 2020," *JAMA Network Open* 5, no. 5 (2022): e2212454, doi: 10.1001/jama networkopen.2022.12454, https://jamanetwork.com/journals/jamanetworkopen/full article/2792372.
- 31 *PORTAL*: See www.PORTAL research.org for a full list of this program's activities.
- 31 "21st Century Cures Act": J. Avorn and A. S. Kesselheim, "The 21st Century Cures Act—Will It Take Us Back in Time?" New England Journal of Medicine 372, no. 26 (June 2015): 2473–475, doi: 10.1056/NEJMp1506964, Epub June 3, 2015, PMID: 26039522, https://pubmed.ncbi.nlm.nih.gov/26039522/.
- 31 marinating in funds from the pharmaceutical lobby: Open Secrets is a Washing-

- ton, D.C.-based nonprofit that tracks political contributions. It notes that pharmaceutical companies "have been among the biggest political spenders for years," and backs that up with data broken down by party and specific recipients. Here is the link to the summary for the industry as a whole: https://www.opensecrets.org/industries/indus?cycle=2024&ind=H4300. Additional tabs there break down contributions by company, lobbying activity, and specific recipients.
- 31 expedited pathways: A. S. Kesselheim et al., "Trends in Utilization of FDA Expedited Drug Development and Approval Programs, 1987–2014: Cohort Study," *BMJ* 351 (2015): h4633, doi: 10.1136/bmj.h4633, https://www.bmj.com/content/351/bmj.h4633.
- 31 *lower standards of evidence*: J. J. Darrow, J. Avorn, and A. S. Kesselheim, "FDA Approval and Regulation of Pharmaceuticals, 1983–2018," *JAMA* 323, no. 2 (2020): 164–76, doi: 10.1001/jama.2019.20288; J. M. Sharfstein, "Reform at the FDA—in Need of Reform," *JAMA* 323, no. 2 (2020): 123–24, doi: 10.1001/jama.2019.20538.
- 33 *Goodhart's law*: Michael F. Stumborg et al., "Goodhart's Law: Recognizing and Mitigating the Manipulation of Measures in Analysis," CNA, September 1, 2022, https://www.cna.org/reports/2022/09/goodharts-law.
- 33 Counting: Deborah Stone, *Counting: How We Use Numbers to Decide What Matters* (New York: Liveright, 2020).
- 33 write a commentary: J. Avorn, "Surrogate Measures of Drug Efficacy—A Finger Pointing at the Moon," *JAMA Network Open* 6, no. 4 (2023): e238835, doi: 10.1001 /jamanetworkopen.2023.8835, https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2804265.
- 34 2024 paper in JAMA: I. T. T. Liu, A. S. Kesselheim, and E. R. S. Cliff, "Clinical Benefit and Regulatory Outcomes of Cancer Drugs Receiving Accelerated Approval," JAMA 331, no. 17 (May 2024): 1471–79, doi: 10.1001/jama.2024.2396, PMID: 38583175, PMCID: PMC11000139, https://pubmed.ncbi.nlm.nih.gov/38583175/.
- 34 effectiveness of parachutes: G. C. S. Smith and J. P. Pell, "Parachute Use to Prevent Death and Major Trauma Related to Gravitational Challenge: Systematic Review of Randomised Controlled Trials," *BMJ* 327 (2003): 1459, doi: 10.1136/bmj.327.7429.1459, PMID: 14684649, PMCID: PMC300808 https://pubmed.ncbi.nlm.nih.gov/14684649/.
- 35 *evidence-based medicine*: The Dynamed platform offers a good, free review of the principles behind evidence-based medicine: "EBM Fundamentals," DynaMed, 2023, https://resources.ebsco.zone/mfe-container/assets/documents/EBM_Fundamentals.pdf.
- 35 such a controlled trial: R. W. Yeh et al., "Parachute Use to Prevent Death and Major Trauma When Jumping from Aircraft: Randomized Controlled Trial," *BMJ* 363 (December 13, 2018): k5094, doi: 10.1136/bmj.k5094, PMID: 30545967, PMCID: PMC6298200. https://pubmed.ncbi.nlm.nih.gov /30545967/. Erratum in *BMJ* 363 (December 18, 2018): k5343, doi: 10.1136/bmj.k5343.
- 36 2012 opinion piece: Scott Gottlieb, "Changing the FDA's Culture," *National Affairs*, Summer 2012, https://www.nationalaffairs.com/publications/detail/changing-the-fdas-culture%20.

- 36 *led by Kesselheim*: K. N. Vokinger et al., "Regulatory Review Duration and Differences in Submission Times of Drugs in the United States and Europe, 2011 to 2020," *Annals of Internal Medicine* 176 (2023): 1413–18, doi: 10.7326/M23-0623, https://www.acpjournals.org/doi/10.7326/M23-0623.
- 36 Joe Ross, and his colleagues: N. S. Downing, A. D. Zhang, and J. S. Ross, "Regulatory Review of New Therapeutic Agents—FDA versus EMA, 2011–2015," New England Journal of Medicine 376 (2017): 1386–87, doi: 10.1056/NEJMc1700103, PMID: 28379798, https://www.nejm.org/doi/full/10.1056/NEJMc1700103.
- 38 analysis of this issue: E. H. Turner et al., "Selective Publication of Antidepressant Trials and Its Influence on Apparent Efficacy," New England Journal of Medicine 358, no. 3 (January 17, 2008): 252–60, doi: 10.1056/NEJMsa065779, PMID: 18199864, https://pubmed.ncbi.nlm.nih.gov/18199864/.
- 40 the magic of the marketplace: Andrew von Eschenbach, "Medical Innovation: How the U.S. Can Retain Its Lead. The FDA should approve drugs based on safety and leave efficacy testing for post-market studies." Wall Street Journal, February 14, 2012, https://www.wsj.com/articles/SB10001424052970203646004577215 403399350874.
- 40 "expanded access": J. J. Darrow et al., "Practical, Legal, and Ethical Issues in Expanded Access to Investigational Drugs," New England Journal of Medicine 372, no. 3 (January 15, 2015): 279–86, doi: 10.1056/NEJMhle1409465, PMID: 25587952, https://pubmed.ncbi.nlm.nih.gov/25587952/.
- 41 *geriatric conditions*: C. M. Quinlan, "When the Epidemic Ends, Our Work Begins: The Pharmacoepidemiology of HIV Primary Care," *Journal of the American Geriatrics Society*, March 11, 2024, doi: 10.1111/jgs.18873, PMID: 38465775, https://agsjournals.onlinelibrary.wiley.com/doi/10.1111/jgs.18873.
- 41 65 percent of new drugs: "New Drug Therapy Approvals 2022: Advancing Health through Innovation," FDA, January 2023, https://www.fda.gov/drugs/novel-drug-approvals-fda/new-drug-therapy-approvals-2022.
- 41 *turn out not to work well*: Liu, Kesselheim, and Cliff, "Clinical Benefit and Regulatory Outcomes of Cancer Drugs Receiving Accelerated Approval."
- 41 *more careful scrutiny*: H. Naci, K. R. Smalley, and A. S. Kesselheim, "Characteristics of Preapproval and Postapproval Studies for Drugs Granted Accelerated Approval by the US Food and Drug Administration," *JAMA* 318, no. 7 (August 15, 2017): 626–36, doi: 10.1001/jama.2017.9415, PMID: 28810023, PMCID: PMC5817559, https://pubmed.ncbi.nlm.nih.gov/28810023/.
- 41 only a fifth of new cancer drugs: B. Gyawali, S. P. Hey, and A. S. Kesselheim, "Assessment of the Clinical Benefit of Cancer Drugs Receiving Accelerated Approval," *JAMA Internal Medicine* 179, no. 1 (July 1, 2019): 906–13, doi: 10.1001/jamainternmed.2019.0462, PMID: 31135808, PMCID: PMC6547118, https://pubmed.ncbi.nlm.nih.gov/31135808/.
- 42 *inspector general*: "Delays in Confirmatory Trials for Drug Applications Granted FDA's Accelerated Approval Raise Concerns," Office of the Inspector General of the Department of Health and Human Services, Washington, D.C., 2022.
- 42 FDA announced new policies: Sydney Lupkin, "FDA Has New Leverage over Com-

panies Looking for a Quicker Drug Approval," NPR, March 3, 2023, https://www.npr.org/sections/health-shots/2023/03/03/1160702899/fda-enforcement-drug-approval-manufacturer-promises.

CHAPTER 2: DECISION-MAKING AND DEMENTIA

- 43 The Ethics of Belief: William K. Clifford in Contemporary Review, 1877; reprinted in Lectures and Essays (London: Macmillan, 1901); cited by Thomas Friedman, New York Times, April 18, 2024.
- 46 A team of investigative reporters: Adam Feuerstein, Matthew Herper, and Damian Garde, "Inside 'Project Onyx': How Biogen Used an FDA Back Channel to Win Approval of Its Polarizing Alzheimer's Drug," STAT, June 29, 2021, https://www.statnews.com/2021/06/29/biogen-fda-alzheimers-drug-approval-aduhelm-project-onyx/.
- 48 As the STAT team reported: Matthew Herper, Damian Garde, and Adam Feuerstein, "Newly Disclosed FDA Documents Reveal Agency's Unprecedented Path to Approving Aduhelm," STAT, June 22, 2021, https://www.statnews.com/2021/06/22/documents-reveal-fda-unprecedented-aduhelm-decision/.
- 50 quit the advisory committee: Bill Chappell, "3 Experts Have Resigned from an FDA Committee over Alzheimer's Drug Approval," NPR, June 11, 2021, https://www.npr.org/2021/06/11/1005567149/3-experts-have-resigned-from-an-fda-committee-over-alzheimers-drug-approval.
- 50 an op-ed in the New York Times: Aaron S. Kesselheim and Jerry Avorn, "The FDA Has Reached a New Low," *New York Times*, June 15, 2021.
- 51 "accelerated withdrawal": P. Whitehouse et al., "Making the Case for Accelerated Withdrawal of Aducanumab," *Journal of Alzheimer's Disease* 87, no. 3 (2022): 1003–7, doi: 10.3233/JAD-220262, PMID: 35404287, https://pubmed.ncbi.nlm.nih.gov/35404287/.
- 52 retracting the paper: Charles Piller, "Researchers Plan to Retract Landmark Alzheimer's Paper Containing Doctored Images," *Science*, June 4, 2024, https://www.science.org/content/article/researchers-plan-retract-landmark-alzheimers-paper-containing-doctored-images.
- 52 problems with the FDA's approval: J. Lenzer and S. Brownlee, "Donanemab: Conflicts of Interest Found in FDA Committee That Approved New Alzheimer's Drug," BMJ 3864 (September 25, 2024): q2010, doi: 10.1136/bmj.q2010, https://www.bmj.com/content/386/bmj.q2010.
- 56 "yes" over 80 percent of the time: Alexandra Pecci, "FDA's 2022 Drug Approvals Fall Short of Recent Norms," PharmaVoice, January 19, 2023, https://www.pharmavoice.com/news/FDA-2022-drug-approvals-fell-by-the-numbers/640690/.
- 56 large randomized clinical trial: C. H. van Dyck et al., "Lecanemab in Early Alzheimer's Disease," New England Journal of Medicine 388, no. 1 (January 5, 2023): 9–21, doi: 10.1056/NEJMoa2212948, PMID: 36449413, https://pubmed.ncbi.nlm.nih.gov/36449413/.
- 57 an op-ed for the Washington Post: Jerry Avorn, "New Alzheimer's Drug Is a Prob-

- lem for FDA's Pass-Fail Approach," *Washington Post*, June 15, 2023, https://www.washingtonpost.com/opinions/2023/06/15/fda-conditional-approval-alzheimers-drug-leqembi/.
- 58 educational materials for prescribers and patients about the drug: See https://alosahealth.org/clinical-modules/dementia/.
- 59 *a genetic trait*: Walt Bogdanich and Carson Kessler, a version of this article appears in print on October 24, 2024, section A, page 1 of the New York edition with the headline, "Drugmakers Had a Secret in Alzheimer's Trials," *New York Times*, October 24, 2024.
- 61 The inspector general concluded: "Delays in Confirmatory Trials for Drug Applications Granted FDA's Accelerated Approval Raise Concerns," Office of the Inspector General of the Department of Health and Human Services, Washington, D.C., September 29, 2022, https://oig.hhs.gov/reports-and-publications/all-reports-and-publications/delays-in-confirmatory-trials-for-drug-applications-granted-fdas-accelerated-approval-raise-concerns/.
- 61 *a congressional investigation*: "Maloney and Pallone Release Staff Report on Review, Approval, and Pricing of Biogen's Alzheimer's Drug Aduhelm," House Committee on Oversight and Accountability (Democrats), December 29, 2022, https://oversightdemocrats.house.gov/news/press-releases/maloney-and-pallone-release-staff-report-on-review-approval-and-pricing-of.
- 62 FDORA: Sydney Lupkin, "FDA Has New Leverage over Companies Looking for a Quicker Drug Approval," NPR, March 2,2023, https://www.npr.org/sections/health-shots/2023/03/03/1160702899/fda-enforcement-drug-approval-manufac turer-promises.
- 62 followup OIG report: "How FDA Used Its Accelerated Approval Pathway Raised Concerns in 3 of 24 Drugs Reviewed," Office of the Inspector General of the Department of Health and Human Services, Washington, D.C., January 14, 2025, https://oig.hhs.gov/reports/all/2025/how-fda-used-its-accelerated-approval-pathway-raised-concerns-in-3-of-24-drugs-reviewed/.
- 62 exit interview with STAT: Sarah Owermohle, "FDA's Woodcock Reflects on More Than 30 Years at Agency—and Hints at What's Next," STAT, January 30, 2024, https://www.statnews.com/2024/01/30/janet-woodcock-fda-next-chapter/.

CHAPTER 3: LOWERING THE BAR

- 65 Its public session in April 2016: Andrew Pollack, "Advisers to FDA. Vote against Duchenne Muscular Dystrophy Drug," New York Times, April 25, 2016, https://www.nytimes.com/2016/04/26/business/muscular-dystrophy-drug-fda-sarepta-eteplirsen.html; Food and Drug Administration, Center for Drug Evaluation and Research, "Summary Minutes of the Peripheral and Central Nervous System Drugs Advisory Committee Meeting," April 25, 2016, https://public4.pagefreezer.com/content/FDA/25-12-2021T00:45/https://www.fda.gov/media/121640/download.
- 66 parents said it would be heartless: Rita Rubin, "Patients' and Parents' Pleas Couldn't Trump Data Concerns at FDA Meeting on Muscular Dystrophy Drug," Forbes, April 16, 2016, https://www.forbes.com/sites/ritarubin/2016/04/26/patients-and

- -parents-pleas-couldnt-trump-data-concerns-at-fda-meeting-on-muscular -dystrophy-drug/?sh=380b54395bde.
- 68 Sarepta "needed to be capitalized": Ben Adams, "No Storm for Sarepta, but Has the FDA Created Its Own Tempest?" Fierce Biotech, September 19, 2016, https://www.fiercebiotech.com/biotech/no-winter-storm-time-for-sarepta-but-has-fda-created-its-own-tempest.
- 68 net revenue of \$1.1 billion: "Sarepta Therapeutics Announces Fourth Quarter and Full-Year 2023 Financial Results and Recent Corporate Developments," Sarepta Therapeutics, February 28, 2024, https://investorrelations.sarepta.com/news-releases/news-release-details/sarepta-therapeutics-announces-fourth-quarter-and-full-year-2023.
- 69 FDA has had no power: There is hope that following the inspector general's scathing review of how the FDA has managed its accelerated approval program, new legislation will give it more authority to withdraw medications that fail to confirm their initial promise. But at present this is just aspirational.
- 69 a series of papers from PORTAL: L. Bendicksen et al., "The Regulatory Repercussions of Approving Muscular Dystrophy Medications on the Basis of Limited Evidence," Annals of Internal Medicine 176, no. 9 (September 2023): 1251–56, doi: 10.7326/M23-1073, Epub August 22, 2023, PMID: 37603868, https://pubmed.ncbi.nlm.nih.gov/37603868/; D. Hong et al., "Characteristics of Patients Receiving Novel Muscular Dystrophy Drugs in Trials vs. Routine Care," JAMA Network Open 7, no. 1 (January 2, 2024): e2353094, doi: 0.1001/jamanetwork open.2023.53094, PMID: 38265797, PMCID: PMC10809016, https://pubmed.ncbi.nlm.nih.gov/38265797/; L. Bendicksen, A. S. Kesselheim, and B. N. Rome, "Spending on Targeted Therapies for Duchenne Muscular Dystrophy," JAMA 331, no. 13 (April 2, 2024): 1151–53, doi: 10.1001/jama.2024.2776, PMID: 38466271/.
- 69 *The Japanese company*: "Viltolarsen (NS-065/NCNP-01) for the Treatment of Duchenne Muscular Dystrophy: Preliminary Results of the Analysis of the Phase III Trial (RACER53 Study)," Nippon Shinyaku, May 27, 2024, https://www.nippon-shinyaku.co.jp/file/download.php?file_id=7613.
- 73 My PORTAL colleagues wrote a compelling op-ed: Liam Bendicksen, Edward Cliff, and Aaron S. Kesselheim, "This Gene Therapy May Not Work. So Why Did the FDA Fully Approve It? The Agency Has Repeatedly Neglected Its Obligation to Ensure That Drugs Are Effective," Washington Post, July 22, 2024, https://www.washingtonpost.com/opinions/2024/07/22/fda-gene-therapy-elevidys/.
- 73 "Peter Marks makes a mockery of scientific reasoning": Jason Mast and Matthew Herper, "Top FDA Official Peter Marks Overruled Staff, Review Team to Approve Sarepta Gene Therapy," STAT, June 20, 2024, https://www.statnews.com/2024/06/20/sarepta-duchenne-elevidys-fda-approval-peter-marks-over ruled-staff/
- 74 *as reported by STAT*: Adam Feuerstein, "Edited Video Stirs Questions over Financial Ties," *Boston Globe*, July 31, 2024, https://www.statnews.com/2024/07/29/sarepta-duchenne-parent-project-muscular-dystrophy/.

- 75 *used the same surrogate measure*: Liu et al., "Clinical Benefit and Regulatory Outcomes of Cancer Drugs Receiving Accelerated Approval."
- 76 five of the FDA's own scientists: M. Merino et al., "Irreconcilable Differences: The Divorce between Response Rates, Progression-Free Survival, and Overall Survival," *Journal of Clinical Oncology* 41, no. 15 (March 17, 2023): 2706–12, doi: 10.1200/JCO.23.00225, https://ascopubs.org/doi/10.1200/JCO.23.00225.
- 76 quality of life: B. Kovic et al., "Evaluating Progression-Free Survival as a Surrogate Outcome for Health-Related Quality of Life in Oncology: A Systematic Review and Quantitative Analysis," *JAMA Internal Medicine* 178, no. 12 (2018): 1586–96, doi: 10.1001/jamainternmed.2018.4710, https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2705082.
- 77 80 to 90 percent of new drug submissions were approved: There is great variability in how the numerator and denominator are defined here, but this is a good approximation. See "Summary of NDA Approvals and Receipts, 1938 to the Present," FDA, January 31, 2018, https://www.fda.gov/about-fda/histories-fda-regu lated-products/summary-nda-approvals-receipts-1938-present.
- 80 decisions that were made right up against the deadline: D. Carpenter, E. J. Zucker, and J. Avorn, "Drug-Review Deadlines and Safety Problems," New England Journal of Medicine 358, no. 13 (March 27, 2008): 1354–61, doi: 10.1056/NE JMsa0706341, PMID: 18367738, https://pubmed.ncbi.nlm.nih.gov/18367738/.
- 80 drugs for rare diseases were being approved: A. S. Kesselheim, J. A. Myers, and J. Avorn, "Characteristics of Clinical Trials to Support Approval of Orphan vs. Nonorphan Drugs for Cancer," *JAMA* 305, no. 22 (June 8, 2011): 2320–26, doi: 10.1001/jama.2011.769, PMID: 21642684, https://pubmed.ncbi.nlm.nih.gov/21642684/.
- 83 The Constitution of Knowledge: Jonathan Rauch, *The Constitution of Knowledge: A Defense of Truth* (Washington, D.C., Brookings Institution Press, 2021).

CHAPTER 4: STANDARDS THAT MATTER TO PATIENTS

- 88 the Oxford researchers: https://www.ox.ac.uk/news/2020-06-16-low-cost-dexa methasone-reduces-death-one-third-hospitalised-patients-severe; RECOVERY Collaborative Group, P. Horby et al., "Dexamethasone in Hospitalized Patients with Covid-19," New England Journal of Medicine 384, no. 8 (February 25, 2021): 693–704, doi: 10.1056/NEJMoa2021436, Epub July 17, 2020, PMID: 32678530, PMCID: PMC7383595, https://pubmed.ncbi.nlm.nih.gov/32678530/.
- 90 releasing some of those vital data: See this paper from PORTAL, which presents a different perspective: C. J. R. Daval and A. S. Kesselheim, "The Origins of 'Confidential Commercial Information' at the FDA," *JAMA* 332, no. 7 (August 20, 2024), doi: 10.1001/jama.2024.9639, PMID: 39037797, https://pubmed.ncbi.nlm.nih.gov/39037797/.
- 92 Alzheimer's drug Leqembi: Jerry Avorn and Alexander Chaitoff, "Registry Enrollment for Alzheimer's Drug Coverage Won't Help Much—A Minimalist Policy for a Minimalist Treatment," MedPage Today, July 11, 2023, https://www.medpagetoday.com/opinion/second-opinions/105427.
- 93 survey of a random sample: S. S. Dhruva et al., "Physicians' Perspectives on FDA

- Regulation of Drugs and Medical Devices: A National Survey," *Health Affairs* 43, no. 1 (January 2024): 27–35, doi: 10.1377/hlthaff.2023.00466, PMID: 38190596, https://pubmed.ncbi.nlm.nih.gov/38190596/.
- 93 "a basketball that's probably going to stay inflated": Richard Morin, "Remembering Deflategate: What Really Happened? Did Tom Brady Cheat with New England Patriots?" USA Today, January 29, 2022, https://www.usatoday.com/story/sports/nfl/2022/01/29/deflategate-explained-did-tom-brady-cheat-new-england-patriots/9274248002/.

CHAPTER 5: HOW DO WE FIND OUT ABOUT DRUG RISKS?

- 100 "Epidemiology in Plato's Cave: Claims Data and Clinical Reality": J. Avorn, "Epidemiology in Plato's Cave: Claims Data and Clinical Reality," Journal of Clinical Epidemiology 44, no. 9 (1991): 867–69, doi: 10.1016/0895-4356(91)90046-c, PMID: 1890429, https://pubmed.ncbi.nlm.nih.gov/1890429/. A related paper from this early period is: J. Avorn, "Medicaid-Based Pharmacoepidemiology: Claims and Counterclaims," Epidemiology 1, no. 2 (March 1990): 98–100, PMID: 2073512, https://pubmed.ncbi.nlm.nih.gov/2073512/.
- 101 well described in an FDA publication: Carol Ballentine, "Taste of Raspberries, Taste of Death: The 1937 Elixir Sulfanilamide Incident," FDA Consumer, June 1981, https://www.fda.gov/about-fda/histories-product-regulation/sulfanilamide -disaster.
- 104 Dr. Kelsey was declared a hero: J. Avorn, "Two Centuries of Assessing Drug Risks," New England Journal of Medicine 367, no. 3 (July 19, 2012): 193–97, doi: 10.1056/NEJMp1206652, PMID: 22808954, https://pubmed.ncbi.nlm.nih.gov/22808954/.
- 111 JAMA published a striking paper: F. E. Silverstein et al., "Gastrointestinal Toxicity with Celecoxib vs. Nonsteroidal Anti-Inflammatory Drugs for Osteoarthritis and Rheumatoid Arthritis: The CLASS Study: A Randomized Controlled Trial. Celecoxib Long-Term Arthritis Safety Study," *JAMA* 284, no. 10 (September 13, 2000): 1247–55, doi: 10.1001/jama.284.10.1247, PMID: 10979111, https://pubmed.ncbi.nlm.nih.gov/10979111/.
- 111 selective inhibition of the study's findings: J. M. Wright et al., "Reporting of 6-Month vs. 12-Month Data in a Clinical Trial of Celecoxib," *JAMA* 286, no. 19 (November 21, 2001): 2398–400, PMID: 11712925, https://pubmed.ncbi.nlm.nih .gov/11712925/.
- 111 coauthored a statement: F. Davidoff et al., "Sponsorship, Authorship, and Accountability," New England Journal of Medicine 345, no. 11 (September 13, 2001): 825–26, discussion 826–27, doi: 10.1056/NEJMed010093, PMID: 11556304, https://pubmed.ncbi.nlm.nih.gov/11556304/.
- 112 published the VIGOR trial: C. Bombardier et al., "Comparison of Upper Gastroin-testinal Toxicity of Rofecoxib and Naproxen in Patients with Rheumatoid Arthritis," New England Journal of Medicine 343, no. 21 (November 23, 2000): 1520–28, 2 p following 1528, doi: 10.1056/NEJM200011233432103, PMID: 11087881, https://pubmed.ncbi.nlm.nih.gov/11087881/.
- 114 poisons the well of trust: A. S. Kesselheim et al., "A Randomized Study of How Phy-

- sicians Interpret Research Funding Disclosures," *New England Journal of Medicine* 367, no. 12 (September 20, 2012): 1119–27, doi: 10.1056/NEJMsa1202397, PMID: 22992075, PMCID: PMC3538846, https://pubmed.ncbi.nlm.nih.gov/22992075/.
- 118 *The DSMB was led*: Snigdha Prakash and Vikki Valentine, "Timeline: The Rise and Fall of Vioxx," NPR, November 10, 2007, https://www.npr.org/2007/11/10/5470430/timeline-the-rise-and-fall-of-vioxx.
- 118 But it didn't correct the paper: G. D. Curfman, S. Morrissey, and J. M. Drazen, "Expression of Concern Reaffirmed," New England Journal of Medicine 354, no. 11 (March 16, 2006): 1193, doi: 10.1056/NEJMe068054, PMID: 16495386, https://pubmed.ncbi.nlm.nih.gov/16495386/.
- 118 cardiologists from the Cleveland Clinic: D. Mukherjee, S. E. Nissen and E. J. Topol, "Risk of Cardiovascular Events Associated with Selective COX-2 Inhibitors," *JAMA* 268, no. 8 (August 22–29, 2001): 954–59, doi: 10.1001/jama.286.8.954, PMID: 11509060, https://pubmed.ncbi.nlm.nih.gov/11509060/.
- "Expressions of Concern": G. D. Curfman, S. Morrissey, and J. M. Drazen, "Expression of Concern: Bombardier et al., 'Comparison of Upper Gastrointestinal Toxicity of Rofecoxib and Naproxen in Patients with Rheumatoid Arthritis,' N Engl J Med 2000;343:1520-8," New England Journal of Medicine 353, no. 26 (December 29, 2005): 2813-14, doi: 10.1056/NEJMe058314, Epub December 8, 2005, PMID: 16339408, https://pubmed.ncbi.nlm.nih.gov/16339408/.

CHAPTER 6: DOWNFALL OF A GIANT

- 120 Here is how the approach works: J. Avorn, "Systematic Detection of Adverse Drug Events," ch. 12, in *Principles of Pharmacology: The Pathophysiologic Basis of Drug Therapy*, 5th ed., ed. D. Golan (Philadelphia: Lippincott Williams & Wilkins, 2025); see also S. Schneeweiss and J. Avorn, "A Review of Uses of Health Care Utilization Databases for Epidemiologic Research on Therapeutics."
- 121 adjust for those differences: S. Schneeweiss et al., "High-Dimensional Propensity Score Adjustment in Studies of Treatment Effects Using Health Care Claims Data," *Epidemiology* 20, no. 4 (July 2009): 512–22, doi: 10.1097/EDE.0b013e 3181a663cc. Erratum in *Epidemiology* 29, no. 6 (November 2018): e63–e64, doi: 10.1097/EDE.00000000000000886, PMID: 19487948, PMCID: PMC3077219.
- 122 our growing field of pharmacoepidemiology: For a good overview, see A. Abbasi et al., "Post-Approval Evidence Generation: A Shared Responsibility for Healthcare," *Nature Medicine* 30, no. 11 (September 13, 2024): 3046–49, doi: 10.1038 //41591-024-03241-x, PMID: 39271845.
- 122 *that research in our program*: A summary of our division's work in this area is at www.harvardpreg.org.
- 128 Singh said that Dr. Lou Sherwood: These facts later came to light in sworn Senate testimony: "FDA, Merck, and Vioxx: Putting Patient Safety First?," U.S. Senate Committee on Finance, November 18, 2004, https://www.finance.senate.gov/hearings/fda-merck-and-vioxx-putting-patient-safety-firstd.
- 129 Circulation . . . accepted the paper: D. H. Solomon et al., "Relationship between Selective Cyclooxygenase-2 Inhibitors and Acute Myocardial Infarction in

- Older Adults," *Circulation* 109, no. 17 (May 4, 2004): 2068–73, doi: 10.1161/01. CIR.0000127578.21885.3E, Epub April 19, 2004, PMID: 15096449, https://pubmed.ncbi.nlm.nih.gov/15096449/.
- 130 an article on the front page of the paper's business section: Thomas M. Burton, "Merck Takes Author's Name off Vioxx Study," *Wall Street Journal*, May 18, 2004, https://www.wsj.com/articles/SB108482794030613720.
- 132 *APPROVe*: R. S. Bresalier et al., "Cardiovascular Events Associated with Rofecoxib in a Colorectal Adenoma Chemoprevention Trial," *New England Journal of Medicine* 352, no. 11 (March 17, 2005): 1092–102, doi: 10.1056/NEJMoa050493, Epub February 15, 2005. PMID: 15713943, https://pubmed.ncbi.nlm.nih.gov/15713943/. Erratum in *New England Journal of Medicine* 355, no. 2 (July 13, 2006): 221.
- 132 they had to take the drug off the market: Terence Neilan, "Merck Pulls Vioxx Painkiller from Market, and Stock Plunges," New York Times, September 30, 2004, https://www.nytimes.com/2004/09/30/business/merck-pulls-vioxx-painkiller-from-market-and-stock-plunges.html.
- 135 paper I wrote with Aaron Kesselheim: A. S. Kesselheim and J. Avorn, "The Role of Litigation in Defining Drug Risks," JAMA 297, no. 3 (January 17, 2007): 308–11, doi: 10.1001/jama.297.3.308, PMID: 17227983, https://pubmed.ncbi.nlm.nih.gov/17227983/.

CHAPTER 7: TEXAS HOLD'EM

- 138 Mark Lanier: See https://www.lanierlawfirm.com/attorneys/w-mark-lanier/.
- 140 What Did They Warn: For a book-length description of the Humeston trial, see Snigdha Prakash, *All the Justice Money Can Buy* (Berkshire, UK: Kaplan, 2011).
- 141 *the company had conducted a trial*: The statements that follow are taken from internal memos discovered by plaintiffs' attorneys through the Vioxx litigation.
- 144 FDA-approved drug labels: W. Shrank et al., "Effect of Content and Format of Prescription Drug Labels on Readability, Understanding, and Medication Use: A Systematic Review," Annals of Pharmacotherapy 41, no. 5 (May 2007): 783–801, doi: 10.1345/aph.1H582, Epub April 10, 2007, PMID: 17426075, https://pubmed.ncbi.nlm.nih.gov/17426075/.
- 146 The jury agreed with our side of the case: "\$47.5 Million Payout in N.J. Vioxx Case," NBC News, March 12, 2007, https://www.nbcnews.com/id/wbna17580006; Associated Press, "In Big Penalty, Jury Reverses a Vioxx Verdict," New York Times, March 13, 2007, https://www.nytimes.com/2007/03/13/business/13vioxx.html. See also J. H. Tanne, "Merck Appeals Rofecoxib Verdict," BMJ 334, no. 7594 (March 24, 2007): 607, doi: 10.1136/bmj.39157.476910.DB, PMID: 17379897, PMCID: PMC1832024, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1832024/.
- 146 "an extreme deviation from reasonable standards of conduct": The University of California San Francisco maintains a remarkable archive of documents related to a wide range of litigation about drugs and other topics of public interest. There is a trove of material on the Humeston case and other Vioxx case-related materials at https://www.industrydocuments.ucsf.edu/drug/collections/vioxx -litigation-documents/. Additional material about Merck's marketing of Vioxx

- is archived at https://www.industrydocuments.ucsf.edu/drug/collections/vioxx -marketing-collection/.
- 149 We published our paper: D. Madigan et al., "Under-Reporting of Cardiovascular Events in the Rofecoxib Alzheimer Disease Studies," American Heart Journal 164, no. 2 (August 2012): 186–93, doi: 10.1016/j.ahj.2012.05.002, Epub July 3, 2012, PMID: 22877803, https://pubmed.ncbi.nlm.nih.gov/22877803/.
- 150 Those results were reported: F. K. Chan et al., "Celecoxib versus Diclofenac and Omeprazole in Reducing the Risk of Recurrent Ulcer Bleeding in Patients with Arthritis," New England Journal of Medicine 347, no. 26 (December 26, 2002): 21041–10, doi: 10.1056/NEJMoa021907, PMID: 12501222, https://pubmed.ncbi.nlm.nih.gov/12501222/.

CHAPTER 8: THE LABEL AS PROTECTIVE TALISMAN

- 154 extra-strength narcotic painkiller: Y. Olsen and J. M. Sharfstein, "Chronic Pain, Addiction, and Zohydro," New England Journal of Medicine 370, no. 22 (May 29, 2014): 2061–63, doi: 10.1056/NEJMp1404181, Epub April 23, 2014, PMID: 24758596, https://pubmed.ncbi.nlm.nih.gov/24758596/.
- 154 the high court didn't see it that way: "Wyeth v. Levine," Cornell Law School Legal Information Institute, https://www.law.cornell.edu/supct/html/06-1249.ZS .html; see also S. David and S. Rosenbaum, "Wyeth v. Levine: Implications for Public Health Policy and Practice," Public Health Reports 125, no. 3 (May–June 2010): 494–97, doi: 10.1177/003335491012500319, PMID: 20433045, PMCID: PMC2848278, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2848278/.
- 157 reject the anti-abortion doctors' case: Mark Sherman, "Unanimous Supreme Court Preserves Access to Widely Used Abortion Medication," Associated Press, June 13, 2024, https://apnews.com/article/supreme-court-abortion-mifepristone-fda-4073b9a7b1cbb1c3641025290c22be2a.
- 158 "dangerous controlled substances": Carl Nasman, "Louisiana Designates Abortion Pills as Controlled Substances," BBC News, May 23, 2024, https://www.bbc.com/news/articles/c722llz5dz3o.

CHAPTER 9: A NEW ERA OF REFORM

- 161 *Project 2025*: Project 2025 Presidential Transition Project, https://www.project 2025.org/about/about-project-2025/.
- 163 Senate Finance Committee held hearings: "FDA, Merck, and Vioxx: Putting Patient Safety First?," U.S. Senate Committee on Finance.
- 164 test the comparative effectiveness and safety of drugs: J. Avorn, "Debate about Funding Comparative-Effectiveness Research," New England Journal of Medicine 360, no. 19 (May 7, 2009): 1927–29, doi: 10.1056/NEJMp0902427, PMID: 19420361, https://pubmed.ncbi.nlm.nih.gov/19420361/.
- 167 FDAAA: J. Avorn, A. Kesselheim, and A. A. Sarpatwari, "The FDA Amendments Act of 2007—Assessing Its Effects a Decade Later," New England Journal of Medicine 379, no. 12 (September 20, 2018): 1097–99, doi: 10.1056/NEJMp1803910, PMID: 30231220, https://pubmed.ncbi.nlm.nih.gov/30231220/.

- 168 an editorial in Circulation: J. Avorn, "Evaluating Drug Effects in the Post-Vioxx World: There Must Be a Better Way," Circulation 113, no. 18 (May 9, 2006): 2173–76, doi: 10.1161/CIRCULATIONAHA.106.625749, PMID: 16684873, https://pubmed.ncbi.nlm.nih.gov/16684873/.
- 168 build a nationwide system: See https://www.sentinelinitiative.org/about and https://www.sentinelinitiative.org/.
- 169 The foundation's website: See https://reaganudall.org/programs/research/post-market-research.
- 170 reanalyzed . . . Avandia: S. E. Nissen and K. Wolski, "Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes," New England Journal of Medicine 356, no. 24 (June 14, 2007): 2457–71, doi: 10.1056/NEJMoa072761, Epub May 21, 2007. PMID: 17517853, https://pubmed.ncbi.nlm.nih.gov/17517853/. Erratum in New England Journal of Medicine 357, no. 1 (July 5, 2007): 100.
- 172 FDAAA changed that: See https://www.clinicaltrials.gov/about-site/selected -publications.
- 172 still very incomplete: J. T. Nelson et al., "Comparison of Availability of Trial Results in ClinicalTrials.gov and PubMed by Data Source and Funder Type," JAMA 329, no. 16 (April 25, 2023): 1404–6, doi: 10.1001/jama.2023.2351, PMID: 36995689, PMCID: PMC10064282, https://pubmed.ncbi.nlm.nih.gov/36995689/. See also: N. J. DeVito, S. Bacon, and B. Goldacre, "Compliance with Legal Requirement to Report Clinical Trial Results on ClinicalTrials.gov: A Cohort Study," Lancet 395, no. 10221 (February 1, 2020): 361–69, doi: 10.1016/S0140-6736(19)33220-9, Epub: January 17, 2020, PMID: 31958402, https://pubmed.ncbi.nlm.nih.gov/31958402/.
- 174 under-completion of such vital studies: B. L. Brown et al., "Fulfillment of Postmarket Commitments and Requirements for New Drugs Approved by the FDA, 2013–2016," *JAMA Internal Medicine* 182, no. 11 (2022): 1223–26, doi:10.1001/ja mainternmed.2022.4226, https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2797103.

CHAPTER 10: THE PRICE OF A WONDER DRUG

- 179 I couldn't afford that: See https://patientsforaffordabledrugs.org/.
- 180 The U.S. spends about 17 percent: Emma Wagner et al., "How Does Health Spending in the U.S. Compare to Other Countries?," Peterson-KFF Health System Tracker, January 23, 2024, https://www.healthsystemtracker.org/chart-collection/health-spending-u-s-compare-countries/#Per%20capita%20health %20expenditures,%20U.S.%20dollars,%20PPP%20adjusted,%202021%20and %202022%C2%A0.
- 180 health outcomes don't lead the pack globally: David Blumenthal et al., "Mirror, Mirror 2024: A Portrait of the Failing U.S. Health System—Comparing Performance in 10 Nations," Commonwealth Fund, September 2024, https://www.commonwealthfund.org/publications/fund-reports/2024/sep/mirror-mirror-2024.
- 181 trouble paying for the prescriptions: Lunna Lopes et al., "Americans' Challenges

- with Health Care Costs," KFF, March 1, 2024, https://www.kff.org/health-costs/issue-brief/americans-challenges-with-health-care-costs/.
- 182 Wonder Drug: Amie Kendall, "Wonder Drug: A Comedy about Cystic Fibrosis," Fringe Review, August 20, 2023, http://fringereview.co.uk/review/edinburgh-fringe/2023/wonder-drug-a-comedy-about-cystic-fibrosis/.
- 185 the gene that caused cystic fibrosis: L. C. Tsui and R. Dorfman, "The Cystic Fibrosis Gene: A Molecular Genetic Perspective," Cold Spring Harbor Perspectives in Medicine 3, no. 2 (February 1, 2013): a009472, doi: 10.1101/cshperspect.a009472, PMID: 23378595, PMCID: PMC3552342, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3552342/.
- 187 "venture philanthropy": "Our Venture Philanthropy Model," Cystic Fibrosis Foundation, https://www.cff.org/about-us/our-venture-philanthropy-model.
- 187 nearly \$10 billion per year: "Vertex Reports Third Quarter 2023 Financial Results," Securities and Exchange Commission, https://www.sec.gov/Archives/edgar/data/875320/000087532023000029/ex-991_q32023.htm; see also https://investors.vrtx.com/news-releases/news-release-details/vertex-reports-first-quarter-2024-financial-results.
- 188 Aurora Biosciences: Andrew Pollack, "Vertex Buys Biotechnology Rival for \$592 Million," New York Times, May 1, 2001, https://www.nytimes.com/2001/05/01/business/technology-vertex-buys-biotechnology-rival-for-592-million.html.
- 188 "Because I can": Zachary Folks, "'Pharma Bro' Martin Shkreli Still Banned for Life from Pharmaceutical Industry," Forbes, January 13, 2024, https://www.forbes .com/sites/zacharyfolk/2024/01/23/pharma-bro-martin-shkreli-still-banned-for -life-from-pharmaceutical-industry/.
- 189 Journal of Cystic Fibrosis: S. Seyoum et al., "Cost Burden among the CF Population in the United States: A Focus on Debt, Food Insecurity, Housing, and Health Services," *Journal of Cystic Fibrosis* 22, no. 3 (May 2023): 471–77, doi: 10.1016/j.jcf.2023.01.002, Epub January 27, 2023, PMID: 36710098, https://pubmed.ncbi.nlm.nih.gov/36710098/.
- 194 \$5,700 for a year's supply: J. Guo et al., "Current Prices versus Minimum Costs of Production for CFTR Modulators," *Journal of Cystic Fibrosis* 21, no. 5 (September 2022): 866–72, doi: 10.1016/j.jcf.2022.04.007, Epub April 16, 2022, PMID: 35440408, https://pubmed.ncbi.nlm.nih.gov/35440408/.
- 195 slash its patient assistance programs: Ed Silverman, "'Caught in the Middle': A Battle between Vertex and Insurers Is Leaving Cystic Fibrosis Patients with Crushing Drug Costs," STAT, February 20, 2023, https://www.statnews.com/pharmalot/2023/02/20/cystic-fibrosis-drug-costs-copays-vertex/.

CHAPTER 11: GIVING IT ALL AWAY

- 199 "a backwater office": Editorial Board, "Save America's Patent System," New York Times, April 16, 2022, https://www.nytimes.com/2022/04/16/opinion/patents -reform-drug-prices.html.
- 203 A JAMA study from Yale: A. S. Long et al., "Evaluation of Trials Comparing Single-Enantiomer Drugs to Their Racemic Precursors: A Systematic Re-

- view," *JAMA Network Open* 4, no. 5 (2021): e215731, doi:10.1001/jamanetworkopen.2021.5731, https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2779579.
- 204 I-MAK (the Initiative for Medicines, Access, and Knowledge): https://www.i-mak .org.
- 204 the productive group at Yale: Yale Collaboration for Regulatory Rigor, Integrity, and Transparency (CRRIT), https://medicine.yale.edu/crrit/.
- 204 helped establish the legal basis for the generic drug industry: Alfred Engelberg, Breaking the Medicine Monopolies: Reflections of a Generic Drug Pioneer (Nashville, TN: Post Hill Press, 2025).
- 204 the relationship between patents and medication access: Robin Feldman, Drugs, Money, and Secret Handshakes (Cambridge, UK: Cambridge University Press, 2019).
- 205 striking report: "Overpatented, Overpriced: Curbing Patient Abuse: Tackling the Root of the Drug Pricing Crisis" (Lewes, DE: Initiative for Medicines, Access, and Knowledge, 2022).
- 210 virtually no new drugs to address novel cellular targets since 1986: William B. Feldman and Aaron S. Kesselheim, "How the Makers of Inhalers Keep Prices so High," *Washington Post*, June 1, 2023.
- 213 *A Sinister HIV Hop?*: Rebecca Rollins and Sheryl Gay Stolberg, "How a Drugmaker Profited by Slow-Walking a Promising HIV Therapy," *New York Times*, July 22, 2023, https://www.nytimes.com/2023/07/22/business/gilead-hiv-drug-tenofovir.html.
- 214 Bayh-Dole Act: Kevin J. Hickey and Emily G. Blevins, "March-In Rights under the Bayh-Dole Act: Draft Guidance," Congressional Research Service, Washington, D.C., 2024, https://crsreports.congress.gov. See also A. Sarpatwari, A. S. Kesselheim, and R. Cook-Deegan, "The Bayh-Dole Act at 40: Accomplishments, Challenges, and Possible Reforms," *Journal of Health Politics, Policy, and Law* 47, no. 6 (December 1, 2022): 879–95, doi: 10.1215/03616878-10041247. PMID: 35877952, https://pubmed.ncbi.nlm.nih.gov/35877952/.
- 214 eminent domain: A. S. Kesselheim and J. Avorn, "Biomedical Patents and the Public's Health: Is There a Role for Eminent Domain?," JAMA 295, no. 4 (2006): 434–37, doi: 10.1001/jama.295.4.434, https://jamanetwork.com/journals/jama/ar ticle-abstract/202235; see also Patrick McGeehan, "Pfizer to Leave City That Won Land-Use Case," New York Times, November 12, 2009, https://www.nytimes.com/2009/11/13/nyregion/13pfizer.html.

CHAPTER 12: A LICENSE TO PRINT MONEY

- 221 forced to limit use of the drug: S. Davey et al., "Changes in Use of Hepatitis C Direct-Acting Antivirals after Access Restrictions Were Eased by State Medicaid Programs," JAMA Health Forum 5, no. 4 (2024): e240302, doi: 10.1001/jama healthforum.2024.0302, https://jamanetwork.com/journals/jama-health-forum/fullarticle/2817286.
- 221 analysis by the Centers for Disease Control: C. Wester et al., "Hepatitis C Virus Clearance Cascade—United States, 2013–2022," Morbidity and Mortality Weekly

- Report 72, No. 26 (June 30, 2023): 716–20, http://dx.doi.org/10.15585/mmwr.mm7226a3, https://www.cdc.gov/mmwr/volumes/72/wr/mm7226a3.htm.
- 222 ferreted out all the patents associated with Sovaldi: R. E. Barenie et al., "Public Funding for Transformative Drugs: The Case of Sofosbuvir," Drug Discovery Today 26, no. 1 (January 2021): 273–81, doi: 10.1016/j.drudis.2020.09.024, Epub October 1 2020, PMID: 33011345, PMCID: PMC7528745, https://pubmed.ncbi.nlm.nih.gov/33011345/.
- 223 The congressional hearings: "The Price of Sovaldi and Its Impact on the U.S. Health Care System," U.S. Senate Committee on Finance, Washington, D.C., 2015, https://www.finance.senate.gov/imo/media/doc/1%20The%20Price%20of%20 Sovaldi%20and%20Its%20Impact%20on%20the%20U.S.%20Health%20Care %20System%20(Full%20Report).pdf.
- 226 \$75 million in public support: B. Gyawali et al., "Government Funding for the Development of Enzalutamide." JAMA Oncol, December 19, 2024. doi: 10.1001/jamaoncol.2024.5661. Epub ahead of print. PMID: 39699929. https://pubmed.ncbi.nlm.nih.gov/39699929/
- 229 The situation on the ground: Teddy Rosenbluth, "UCLA's Fight to Patent a Life-Saving Cancer Drug Could Make the Medicine Virtually Unobtainable in India," Los Angeles Magazine, January 7, 2020, https://lamag.com/featured/ucla-xtandi-india; see also Helen Santoro, "UCLA Benefits Handsomely from Xtandi Cancer Drug Royalties amid Controversy over Drug Pricing," Los Angeles Magazine, April 18, 2024, https://lamag.com/health/ucla-benefits-handsomely-from-xtandi-cancer-drug-royalties-amid-controversy-over-drug-pricing.
- 231 *a letter to the secretary of Health and Human Services*: Claire Cassedy, "Harvard Academics' Letter Supporting Use of U.S. Government Rights in Xtandi Patents to Remedy Price Discrimination against U.S. Residents," Knowledge Ecology International, February 3, 2022, https://www.keionline.org/37323; see also https://www.keionline.org/?s=xtandi.
- 231 public funding was common: R. K. Nayak, J. Avorn, and A. S. Kesselheim, "Public Sector Financial Support for Late Stage Discovery of New Drugs in the United States: Cohort Study," BMJ 367 (October 23, 2019): 15766, doi: 10.1136/bmj.15766, PMID: 31645328, PMCID: PMC6812612, https://pubmed.ncbi.nlm.nih.gov/31645328/.
- 233 "Trade Public Risk for Private Reward": J. Avorn and A. S. Kesselheim, "The NIH Translational Research Center Might Trade Public Risk for Private Reward," Nature Medicine 17, no. 10 (October 11, 2011): 1176, doi: 10.1038/nm1011-1176, PMID: 21988983, https://pubmed.ncbi.nlm.nih.gov/21988983/.
- 234 "Fewer Cures for Patients": Richard Payerchin, "House Republicans Rip Prospect of Medicare Drug Price Negotiations," Medical Economics, September 21, 2023, https://www.medicaleconomics.com/view/house-republicans-rip-prospect-of-medicare-drug-price-negotiations.
- 235 an erroneous industry-funded number: J. Avorn, "The \$2.6 Billion Pill—Methodologic and Policy Considerations," New England Journal of Medicine 372, no. 20 (May 14, 2015): 1877–79, doi: 10.1056/NEJMp1500848, PMID: 25970049, https://pubmed.ncbi.nlm.nih.gov/25970049/.

- 235 plow back only 10 to 15 percent of their revenues into research: The most recent estimate of this is: A. Sertkaya et al., "Costs of Drug Development and Research and Development Intensity in the U.S., 2000–2018, JAMA Network Open 7, no. 6 (2024): e2415445, doi: 10.1001/jamanetworkopen.2024.15445, https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2820562. This paper also provides a comprehensive estimate of the cost of developing a new drug—including the cost of failures—that is only about a third of industry estimates.
- 236 Tauzin announced he would retire from Congress: Olga Pierce, "Medicare Drug Planners Now Lobbyists, with Billions at Stake," ProPublica, October 20, 2009, https://www.propublica.org/article/medicare-drug-planners-now-lobbyists-with -billions-at-stake-1020.
- 237 the chutzpah underlying the largesse: Victoria Knight, Rachana Pradhan, and Elizabeth Lucas, "Pharma Campaign Cash Delivered to Key Lawmakers with Surgical Precision," KFF Health News, October 27, 2021, https://kffhealthnews.org/news/article/pharma-campaign-cash-delivered-to-key-lawmakers-with-surgical-precision/; see also Isaiah Poritz, "Pharmaceutical Industry Backs Democratic Holdouts on Drug Pricing Plan," OpenSecrets, September 17, 2021, https://www.opensecrets.org/news/2021/09/pharmaceutical-industry-backs-democratic-holdouts-on-drug-pricing-plan/.
- 244 *quality-adjusted life-year*: S. D. Pearson, "Why the Coming Debate over the QALY and Disability Will Be Different," *Journal of Law, Medicine & Ethics* 47, no. 2 (June 2019): 304–7, doi: 10.1177/1073110519857286, PMID: 31298099, https://icer.org/wp-content/uploads/2020/10/Pearson-ASLME-article-on-QALY-and-disability.pdf.
- 248 "value flower": P. J. Neumann, L. P. Garrison, and R. J. Willke, "The History and Future of the 'ISPOR Value Flower': Addressing Limitations of Conventional Cost-Effectiveness Analysis," Value Health 25, no. 4 (April 2022): 558–65, doi: 10.1016/j.jval.2022.01.010, Epub March 9, 2022, PMID: 35279370, https://pubmed.ncbi.nlm.nih.gov/35279370/.
- 249 an ongoing process of comparative effectiveness research: J. Avorn, "Debate about Funding Comparative-Effectiveness Research."
- 250 "Legislating against Use of Cost-Effectiveness Information": P. J. Neumann and M. C. Weinstein, "Legislating against Use of Cost-Effectiveness Information," New England Journal of Medicine 363, no. 16 (October 14, 2010): 1495–97, doi: 10.1056/NEJMp1007168, PMID: 20942664, https://pubmed.ncbi.nlm.nih.gov/20942664/.
- 251 the National Academy for State Health Policy: https://nashp.org/.
- 252 PIPC played the race card: "Issue Brief: Traditional Value Assessment Methods Fail Communities of Color and Exacerbate Health Inequities," Partnership to Improve Patient Care, September 28, 2020, https://www.pipcpatients.org/resources/issue-brief-traditional-value-assessment-methods-fail-communities-of-color-and-exacerbate-health-inequities.
- 253 the Colorado State Prescription Drug Affordability Board: Andrew Perez, "Colorado Is Trying to Cap a Drug's Price. Big Pharma Has Other Plans," Rolling

- *Stone*, February 28, 2024, https://www.rollingstone.com/politics/politics-features/colorado-drug-price-enbrel-pharma-1234977554/.
- 254 *A local network affiliate*: https://www.cbsnews.com/colorado/video/patients -doctors-worry-miracle-drug-may-no-longer-be-available-in-colorado/.
- 255 the NHS announced that it would back down: Tristan Manalac, "Vertex Finally Reaches Pricing Deal with England's NHS for Cystic Fibrosis Drugs," BioSpace, June 21, 2024, https://www.biospace.com/vertex-reaches-pricing-deal-with-en gland-s-nhs-for-cystic-fibrosis-drug; see also National Institute for Health and Care Excellence, Final Draft Guidance: Ivacaftor-Tezacaftor-Elexacaftor, Tezacaftor-Ivacaftor, and Lumacaftor-Ivacaftor for Treating Cystic Fibrosis (London: NICE, 2024), https://www.nice.org.uk/guidance/ta988/documents/674.

CHAPTER 14: CONFLICTED INTERESTS

- 258 series by the Boston Globe: Liz Kowalczyk et al., "Boston's Hospital Chiefs Moonlight on Corporate Boards at Rates Far beyond the National Level," Boston Globe, April 3, 2021, https://www.bostonglobe.com/2021/04/03/metro/bostons-hospital-chiefs-moonlight-corporate-boards-rates-far-beyond-national-rate /?event=event12.
- 260 the paper did a 2024 follow-up analysis: Liz Kowalczyk, "Boston's Hospital Chiefs Have Turned Away from Sitting on Outside Boards," Boston Globe, January 31, 2024, https://www.bostonglobe.com/2024/01/31/metro/boston-hospital-chiefs -outside-boards/.
- 261 part-time service on the corporate boards of two drug companies: Elizabeth Koh, "Corporate Compensation for Harvard's New Interim President Stands Out among Ivy League Peers," Boston Globe, January 5, 2024, https://www.bostonglobe.com/2024/01/05/metro/alan-garber-harvard-interim-president/.
- 262 a remarkably generous donor: "Len Blavatnik," Wikipedia, https://en.wikipedia .org/wiki/Len_Blavatnik; see also https://otd.harvard.edu/accelerators/blavatnik -biomedical-accelerator/.
- 265 a book of solid recommendations: Institute of Medicine (U.S.) Committee on Standards for Developing Trustworthy Clinical Practice Guidelines, Clinical Practice Guidelines We Can Trust, eds. R. Graham et al. (Washington, D.C.: National Academies Press, 2011), PMID: 24983061, https://pubmed.ncbi.nlm.nih.gov/24983061/.
- 266 measured how long each disclosure slide was shown: S. Martin and D. P. J. Hunt, "Assessment of Comprehensibility of Industry Conflicts of Interest and Disclosures by Multiple Sclerosis Researchers at Medical Conferences," *JAMA Network Open* 4, no. 4 (2021): e212167, doi: 10.1001/jamanetworkopen.2021.2167, https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2778147

CHAPTER 15: MAKING MEDICINES AFFORDABLE

268 devote far more resources to lobbying: O. J. Wouters, "Lobbying Expenditures and Campaign Contributions by the Pharmaceutical and Health Product Industry in the United States, 1999–2018," JAMA Internal Medicine 180, no. 5 (2020): 688–97, doi: 10.1001/jamainternmed.2020.0146, https://jamanetwork.com

- /journals/jamainternalmedicine/fullarticle/2762509. See also "Pharmaceutical Manufacturing Lobbying," OpenSecrets, https://www.opensecrets.org/industries /lobbying?ind=H4300. See also Statista Research Department, "Leading Lobbying Industries in the U.S. 2023," Statista, July 5, 2024, https://www.statista.com/statistics/257364/top-lobbying-industries-in-the-us/.
- 268 *DoPE*: See www.DrugEpi.org; *Kesselheim's PORTAL*: See www.PORTALresearch .org.
- 269 their eponymous foundation: https://www.arnoldventures.org/.
- 270 errors in defining the end date: S. S. Tu et al., "The Cost of Drug Patent Expiration Date Errors," Nature Biotechnology 42, no. 7 (July 2024): 1024–25, doi: 10.1038/s41587-024-02298-w, PMID: 39020202, https://pubmed.ncbi.nlm.nih.gov/39020202/
- 272 recent court filing: "Brief of 14 Professors of Medicine and Law as Amicus Curiae in Support of Defendants-Appelles" in Teva Branded Pharm. Prods. R&D v. Amneal Pharm. of N.Y., Civil Action 23-20964 (SRC), (D.N.J. September 6, 2024).
- 272 *colleagues at I-MAK*: See Initiative for Medicines, Access, and Knowledge, www.I-MAK.org
- 273 legal strategies the executive branch could use: A. B. Engelberg, J. Avorn, and A. S. Kesselheim, "A New Way to Contain Unaffordable Medication Costs—Exercising the Government's Existing Rights," New England Journal of Medicine 386, no. 12 (March 24, 2022): 1104–6, doi: 10.1056/NEJMp2117102, Epub February 9, 2022, PMID: 35139270, https://pubmed.ncbi.nlm.nih.gov/35139270/.
- 276 VA drug expenditures: B. Venker, K. B. Stephenson, and W. F. Gellad, "Assessment of Spending in Medicare Part D if Medication Prices from the Department of Veterans Affairs Were Used," JAMA Internal Medicine 179, no. 3 (March 1, 2019): 431–33, doi: 10.1001/jamainternmed.2018.5874, PMID: 30640367, PMCID: PMC6439699, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6439699/.
- 277 We don't have to start from scratch on this: Thomas Waldrop, "Value-Based Pricing of Prescription Drugs Benefits Patients and Promotes Innovation," Center for American Progress, September 13, 2021, https://www.americanprogress.org/article/value-based-pricing-prescription-drugs-benefits-patients-promotes-innovation/. See also Richard G. Frank, Jerry Avorn, and Aaron S. Kesselheim, "What Do High Drug Prices Buy Us?" Health Affairs, April 29, 2020, https://www.healthaffairs.org/content/forefront/do-high-drug-prices-buy-us.
- 278 a not-for-profit generic drug company: https://civicarx.org/.
- 279 bring down the cost of creating such new gene therapy: https://innovativegenomics.org/.
- 279 *nonprofit on the far edge of innovative treatments*: https://odylia.org/.
- 280 the 340B designation: I. T. T. Liu et al., "Commercial Markups on Pediatric Oncology Drugs at 340B Pediatric Hospitals," Pediatric Blood & Cancer 71, no. 9 (2024): e31158, https://doi.org/10.1002/pbc.31158.
- 282 scathing reports about the often-overlooked industry: "FTC Releases Interim Staff Report on Prescription Drug Middlemen," Federal Trade Commission, July 9, 2024, https://www.ftc.gov/news-events/news/press-releases/2024/07/ftc-releases

- -interim-staff-report-prescription-drug-middlemen-staff-report.pdf. See also "Hearing Wrap-Up: Oversight Committee Exposes How PBMs Undermine Patient Health and Increase Drug Costs," House Committee on Oversight and Accountability, July 23, 2024, https://oversight.house.gov/release/hearing-wrap-up-oversight-committee-exposes-how-pbms-undermine-patient-health-and-increase-drug-costs/. See also "Prescription Drugs: Selected States' Regulation of Pharmacy Benefit Managers," U.S. Government Accountability Office, April 15, 2024, https://www.gao.gov/products/gao-24-106898.
- 282 Cost Plus Drugs: https://costplusdrugs.com/.
- 282 could have spent \$3.6 billion less each year: H. S. Lalani, A. S. Kesselheim, and B. N. Rome, "Potential Medicare Part D Savings on Generic Drugs from the Mark Cuban Cost Plus Drug Company," Annals of Internal Medicine 175, no. 7 (July 2022): 1053–55, doi: 10.7326/M22-0756, https://pubmed.ncbi.nlm.nih.gov/35724381/.
- 283 an investigative report: Rebecca Robbins and Reed Abelson, "The Opaque Industry Secretly Inflating Prices for Prescription Drugs," New York Times, June 21, 2024, https://www.nytimes.com/2024/06/21/business/prescription-drug-costs-pbm.html. See also "Specialty Generic Drugs: A Growing Profit Center for Vertically Integrated Pharmacy Benefit Managers," Federal Trade Commission Second Interim Staff Report, January 2025, https://www.ftc.gov/system/files/ftc_gov/pdf/PBM-6b-Second-Interim-Staff-Report.pdf.
- 286 two astonishing accounts: Jeffrey Flier, "How Pfizer Ended Up Passing on My GLP-1 Work Back in the Early '90s," STAT, September 9, 2024, https://www.stat news.com/2024/09/09/g|p-1-history-pfizer-john-baxter-jeffrey-flier-calbio-me tabio/; Jeffrey S. Flier, "Drug Development Failure: How GLP-1 Development Was Abandoned in 1990," Perspectives in Biology and Medicine 67, no. 3 (Summer 2024): 325–36, https://dx.doi.org/10.1353/pbm.2024.a936213, https://muse.jhu.edu/article/936213.
- 290 an angry op-ed in USA Today: Joe Biden and Bernie Sanders, "Novo Nordisk, Eli Lilly Must Stop Ripping Off Americans with High Drug Prices," USA Today, July 2, 2024, https://www.usatoday.com/story/opinion/2024/07/02/biden-sanders -prescription-drug-cost-ozempic-wegovy/74232827007/.

CHAPTER 16: A FAILURE TO COMMUNICATE

- 297 \$50 billion annual promotion budget: L. M. Schwartz and S. Woloshin, "Medical Marketing in the United States, 1997–2016," *JAMA* 321, no. 1 (January 1, 2019): 80–96, doi: 10.1001/jama.2018.19320, PMID: 30620375, https://pubmed.ncbi.nlm.nih.gov/30620375/.
- 302 *in a surprise decision*: Katie Thomas, "Ruling Is Victory for Drug Companies in Promoting Medicine for Other Uses," *New York Times*, December 3, 2012, https://www.nytimes.com/2012/12/04/business/ruling-backs-drug-industry-on-off-label-marketing.html. See also A. S. Kesselheim, M. M. Mello, and J. Avorn, "FDA Regulation of Off-Label Drug Promotion under Attack," *JAMA* 309, no. 5 (February 6, 2013): 445–46, doi: 10.1001/jama.2012.207972, PMID: 23385267, https://pubmed.ncbi.nlm.nih.gov/23385267/.

- 303 its title summed up the situation neatly: J. Avorn, A. Sarpatwari, and A. S. Kesselheim, "Forbidden and Permitted Statements about Medications—Loosening the Rules," New England Journal of Medicine 373, no. 10 (September 3, 2015): 967–73, doi: 10.1056/NEJMhle1506365, PMID: 26332553, https://pubmed.ncbi.nlm.nih.gov/26332553/.
- 304 The frontispiece of the 1651 edition: https://devonandexeterinstitution.org /wp-content/uploads/2021/02/2.jpg&tbnid=FJV9gwH3KkZDpM&vet=1&img refurl=https://devonandexeterinstitution.org/the-frontispiece-as-a-threshold -of-interpretation-thomas-hobbes-leviathan-1651/&docid=eZvQOmNhJe_uL M&w=1619&h=1355&source=sh/x/im/m1/1&kgs=6a22f55c9bc5ef4d&shem =abme,trie.
- 304 *an article in the* Annals of Internal Medicine: J. Avorn, "In Opposition to Liberty: We Need a 'Sovereign' to Govern Drug Claims," *Annals of Internal Medicine* 163, no. 3 (August 4, 2015): 229–30, doi: 10.7326/M15-1429, PMID: 26121615, https://pubmed.ncbi.nlm.nih.gov/26121615/.
- 306 FDA actions against drugmakers: S. Liu, M. M. Mello, and A. S. Kesselheim, "Prospects for Enforcing Prohibitions on Off-Label Drug Promotion after United States v. Caronia: An Analysis of Litigated Cases," Journal of Health Politics, Policy, and Law 46, no. 3 (June 1, 2021): 487–504, doi: 10.1215/03616878-8893571, PMID: 33647951, https://pubmed.ncbi.nlm.nih.gov/33647951/.
- 307 requiring a company to make certain statements: J. Avorn, "Wedding Websites, Free Speech, and Adverse Drug Effects," New England Journal of Medicine 389, no. 16 (October 19, 2023): 1447–49, doi: 10.1056/NEJMp2307908, Epub October 14, 2023, PMID: 37843109, https://pubmed.ncbi.nlm.nih.gov/37843109/.

CHAPTER 17: SHAPING THE PRESCRIBERS OF TOMORROW

311 The Doctor by Sir Luke Fildes: A. C. Kao, "What Is Represented 'Worthily' in Luke Fildes' The Doctor?," AMA Journal of Ethics 24, no. 7 (July 1, 2022): e697–E713, doi: 10.1001/amajethics.2022.697, PMID: 35838401, https://pubmed.ncbi.nlm.nih.gov/35838401/; https://journalofethics.ama-assn.org/gallery/what-represented-worthily-luke-fildes-doctor.

CHAPTER 18: BETTER SIGNALS

- 334 test it in a randomized controlled trial: J. Avorn and S. B. Soumerai, "Improving Drug-Therapy Decisions through Educational Outreach. A Randomized Controlled Trial of Academically Based 'Detailing," New England Journal of Medicine 308, no. 24 (June 16, 1983): 1457–63, doi: 10.1056/NEJM198306163082406, PMID: 6406886, https://pubmed.ncbi.nlm.nih.gov/6406886/.
- 334 Good Evidence Doesn't Disseminate Itself: This is Avorn's Tenth Law. I'm not sure what the first nine are.
- 334 using population-based data from health-care systems: Jerry Avorn, "Interventional Pharmacoepidemiology: Origins, Current Status, and Future Possibilities," American Journal of Epidemiology (October 10, 2024), https://academic.oup.com/aje/advance-article/doi/10.1093/aje/kwae383/7817814.

- 335 randomized trial in nursing homes: J. Avorn et al., "A Randomized Trial of a Program to Reduce the Use of Psychoactive Drugs in Nursing Homes," New England Journal of Medicine 327, no. 3 (July 16, 1992): 168–73, doi: 10.1056/NEJM 199207163270306, PMID: 1608408, https://pubmed.ncbi.nlm.nih.gov/1608408/.
- 335 systematic reviews: M. A. O'Brien et al., "Educational Outreach Visits: Effects on Professional Practice and Health Care Outcomes," Cochrane Database of Systematic Reviews 2007, no. 4 (October 17, 2007): CD000409, doi: 10.1002/14651858. CD000409.pub2, PMID: 17943742, PMCID: PMC7032679, https://pubmed.ncbi.nlm.nih.gov/17943742/. See also B.N. Rome et al., "Academic Detailing Interventions and Evidence-Based Prescribing: A Systematic Review," JAMA Netw Open. January 2, 2025, 8(1):e2453684, doi: 10.1001/jamanetworkopen.2024.53684. PMID: 39775805, https://pubmed.ncbi.nlm.nih.gov/39775805/.
- 336 *Veterans Affairs health systems*: https://www.pbm.va.gov/PBM/academicdetailing service/AboutUs.asp.
- 337 our new counter-current nonprofit: See www.AlosaHealth.org.
- 338 *a front-page story*: Scott Hensley, "As Drug Bill Soars, Some Doctors Get an 'Unsales' Pitch: Harvard Professor Helps Team in Pennsylvania Publicize Alternatives to Pricey Pills," *Wall Street Journal*, March 13, 2006, https://www.wsj.com/articles/SB114221796975796288. See also Avorn, "Interventional Pharmacoepidemiology."
- 339 evidence-based practical recommendations: https://alosahealth.org/clinical-mod ules/.

CHAPTER 19: ACID REDUX: THE DEATH AND REBIRTH OF PSYCHEDELICS

- 356 *Treatment sessions at Spring Grove*: Jerry Avorn, "Beyond Dying," *Harper's*, March 1973, https://harpers.org/archive/1973/03/beyond-dying/.
- 363 the Multidisciplinary Association for Psychedelic Studies: https://maps.org/about-maps/.
- 364 Boston Psychedelic Research Group: https://www.bostonpsychedelicresearchgroup.com/.
- 373 journal Nature Medicine in September 2023: J. M. Mitchell et al., "MDMA-AssistedTherapyforModeratetoSeverePTSD:ARandomized,Placebo-Controlled Phase 3 Trial," Nature Medicine 29, no. 10 (October 2023): 2473–80, doi: 10.1038/s41591-023-02565-4, Epub September 14, 2023, PMID: 37709999, PMCID: PMC10579091, https://pubmed.ncbi.nlm.nih.gov/37709999/.
- 374 "substantial concerns about the validity of the results": R. A. Mustafa et al., Midomafetamine-Assisted Psychotherapy for Post-Traumatic Stress Disorder: Final Evidence Report (Institute for Clinical and Economic Review, June 27, 2024), https://icer.org/assessment/ptsd-2024/#overview; https://icer.org/wp-content/uploads/2024/06/PTSD_Final-Report_For-Publication_06272024.pdf.
- 374 citizen petition: Neşe Devenot et al., "Citizen Petition to FDA Commissioner," Regulations.gov, April 28, 2024, https://www.regulations.gov/document/FDA -2024-P-2148-0001.

- 375 the FDA advisory committee met in early June: Kai Kupferschmidt, "In a Setback for Psychedelic Therapy, FDA Advisers Vote against Medical Use of Ecstasy," *Science*, June 5, 2024, https://www.science.org/content/article/fda-advisory-panel-rejects-mdma-ptsd-treatment.
- 376 The FDA did indeed follow that advice: Kai Kupferschmidt, "FDA Rejected MDMA-Assisted PTSD Therapy. Other Psychedelics Firms Intend to Avoid That Fate," Science, August 12, 2024, https://www.science.org/content/article/fda -rejected-mdma-assisted-ptsd-therapy-other-psychedelics-firms-intend-avoid -fate.
- 376 "changing the goalposts": Meghana Keshavan, "Rick Doblin, 'Unleashed,' Blasts FDA over Lykos Drug Rejection and Turns to Global Push for MDMA Therapy," STAT, August 17, 2024, https://www.statnews.com/2024/08/17/mdma-psychedelics-rick-doblin-lykos-exit/.
- 379 the city of Denver: Gregory Ferenstein, "A Glimpse into Colorado's Emerging Legal Psychedelics Scene," Reason magazine, July 10, 2024, https://reason.org/commentary/a-glimpse-into-colorados-emerging-legal-psychedelics-scene/.
- 379 the Dutch Committee on MDMA: Mari Eccles, "Dutch Committee Recommends MDMA for Post-Traumatic Stress Disorder," Politico, June 6, 2024, https://www.politico.eu/article/dutch-panel-recommends-mdma-ecstasy-post-traumatic-stress-disorder/. See also Wim van den Brink, "Report of the Dutch State Committee on MDMA: A Summary of Findings and Recommendations," Drug Science, June 19, 2024, https://www.drugscience.org.uk/mdma-netherlands-report.

CHAPTER 20: PAIN, KILLERS

- 383 FDA laid the groundwork: Bill Whitaker, "Did the FDA Ignite the Opioid Epidemic?," 60 Minutes, February 24, 2019, https://www.cbsnews.com/news/opioid-epidemic-did-the-fda-ignite-the-crisis-60-minutes/. See also Gerald Posner, "FDA's Janet Woodcock Failed to Stop the Opioid Epidemic," USA Today, February 3, 2021, https://www.usatoday.com/story/opinion/2021/02/03/janet-woodcocks-failure-fda-opioid-epidemic-column/4352787001/.
- 384 the SPACE trial: E. E. Krebs et al., "Effect of Opioid vs. Nonopioid Medications on Pain-Related Function in Patients with Chronic Back Pain or Hip or Knee Osteoarthritis Pain: The SPACE Randomized Clinical Trial," JAMA 319, no. 9 (March 6, 2018): 872–82, doi: 10.1001/jama.2018.0899, PMID: 29509867, PMCID: PMC5885909, https://pubmed.ncbi.nlm.nih.gov/29509867/.
- 387 "the Jick paper": https://www.nejm.org/doi/pdf/10.1056/NEJM198001103020221.
- 388 A follow-up letter to the NEJM in 2017: P. T. M. Leung et al., "A 1980 Letter on the Risk of Opioid Addiction," New England Journal of Medicine 376, no. 22 (June 1, 2017): 2194–95, doi: 10.1056/NEJMc1700150, PMID: 28564561, https://pubmed.ncbi.nlm.nih.gov/28564561/.
- 389 *a high-flying Arizona start-up*: *Frontline*, season 2020, episode 15, "Opioids, Inc.," produced by Tom Jennings, Annie Wong, and Nick Verbitsky, aired June 23, 2021, on PBS, https://www.pbs.org/wgbh/frontline/documentary/opioids-inc/.
- 390 scathing JAMA paper: J. E. Rollman et al., "Assessment of the FDA Risk Eval-

uation and Mitigation Strategy for Transmucosal Immediate-Release Fentanyl Products," *JAMA* 321, no. 7 (2019): 676–85, doi: 10.1001/jama.2019.0235, https://pmc.ncbi.nlm.nih.gov/articles/PMC6439622/.

CHAPTER 21: YOU CAN'T GET YOUR MEDICINES IF YOU CAN'T GET HEALTH CARE

- 408 The opening salvo of the revolution: J. Agretelis et al., "For Our Patients, Not for Profits: A Call to Action," JAMA 278, no. 21 (1997): 1733–38, doi: 10.1001/jama.1997.03550210031020, https://jamanetwork.com/journals/jama/article-abstract/419060; https://pubmed.ncbi.nlm.nih.gov/9388138/.
- 409 degradation of the doctor-patient relationship: Bernard Lown, The Lost Art of Healing: Practicing Compassion in Medicine (New York: Random House, 1999).
- 425 extensive reporting by the Boston Globe: Elizabeth Koh, Chris Serres, Jessica Bartlett, and Mark Arsenault, "Timeline: Steward Health Care Kept Expanding, Even as the Situation Turned Dire," Boston Globe, September 6, 2024, https://apps.bostonglobe.com/metro/investigations/spotlight/2024/09/steward-hospitals/timeline/.
- 425 Steward and Cerberus: Robert Weisman, "Cerberus Says Its Investment in Steward Hospitals Yielded an \$800 Million Profit," Boston Globe, April 2, 2024, https://www.bostonglobe.com/2024/04/02/business/cerberus-capital-management-steward-health-care/. See also Robert Kuttner, "Steward Health Care Should Face a Full-Scale Criminal Investigation," Boston Globe, February 29, 2024, https://www.bostonglobe.com/2024/02/29/opinion/steward-health-care-criminal-investigation/.
- 426 the company's corporate jets: Excellent coverage of the Steward fiasco has been provided by the Spotlight Team of the Boston Globe. See, for example, Hanna Krueger, Yoohyun Jung, and Brendan McCarty, "For Steward CEO: Jet Travel, Yacht Adventures," Boston Globe, September 19, 2024, https://apps.bostonglobe.com/metro/investigations/spotlight/2024/09/steward-hospitals/flights/.
- 428 hard to find a primary care provider: "A Dire Diagnosis: The Declining Health of Primary Care in Massachusetts and the Urgent Need for Action," Massachusetts Health Policy Commission, January 2025, https://masshpc.gov/sites/default/files/HPC Chartpack_A Dire Diagnosis The Declining Health of Primary Care in MA_0.pdf
- 429 growing influence: A. S. Relman, "The New Medical-Industrial Complex," New England Journal of Medicine 303, no. 17 (October 23, 1980): 963–70, doi: 10.1056 /NEJM198010233031703, PMID: 7412851, https://pubmed.ncbi.nlm.nih.gov/7412851/.

APPENDIX A: RESOURCES FOR CONSUMERS

446 Affording your medications: See H.S. Lalani et al., "Strategies to Help Patients Navigate High Prescription Drug Costs," *JAMA* 332, no. 20 (November 26, 2024): 1741–49, doi: 10.1001/jama.2024.17275, PMID: 39432312, https://pubmed.ncbi.nlm.nih.gov/39432312/. For patients: K.L. Walter, "Strategies to Help Patients Afford Their Medicines in the US." *JAMA*. 2024; 332, no. 20 (October 21, 2024): 1767–68, doi: 10.1001/jama.2024.21143. https://jamanetwork.com/journals/jama/fullarticle/2825161.