Magic Bullets and Wonder Pills: Making Drugs and Diseases in the Twentieth Century

BY BRUNO J. STRASSER*

Robert Bud. *Penicillin: Triumph and Tragedy*. Oxford: Oxford University Press, 2007. 344 pp., illus. ISBN 978-0-19-925406-4. $46 (hardcover).

Jeremy A. Greene. *Prescribing by Numbers: Drugs and the Definition of Disease*. Baltimore: Johns Hopkins University Press, 2007. 336 pp., illus. ISBN 978-0-8018-8477. $42.70 (hardcover).

John E. Lesch. *The First Miracle Drugs: How the Sulfa Drugs Transformed Medicine*. Oxford: Oxford University Press, 2007. 376 pp., illus. ISBN 978-0-19-518775-5. $59.50 (hardcover).

Elizabeth Siegel Watkins. *The Estrogen Elixir: A History of Hormone Replacement Therapy in America*. Baltimore: Johns Hopkins University Press, 2007. 368 pp. ISBN 978-0-8018-8602-7. $37.10 (hardcover).

In 2007 the pharmaceutical industry struggled to bring new drugs onto the market. For historians of science and medicine it was a much more rewarding year. An unprecedented number of new books on the history of drugs have appeared, and more are in the pipeline. Even though the profits of scholarship are undoubtedly more modest, these histories greatly enrich our understanding of current debates on declining returns on investments in pharmaceutical innovation, rising costs of drugs in health care, and the broadening of pathological categories. They also illuminate how and why drugs have become an

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Historical Studies in the Natural Sciences, Vol. 38, Number 2, pps. 303–312. ISSN 1939-1811, electronic ISSN 1939-182X. DOI: 10.1525/hsns.2008.38.2.303.

essential part of our cultural diet. Finally, these new histories of drugs show vividly how the historiography of science and medicine can encompass the relationships among the laboratory, the clinic, the factory, and the marketplace in the production of knowledge.

But what exactly is a "history of a drug" a history of? The most common answer—that it is a history of the drug's active molecule—has proved to be a misleading simplification. The standard narrative of the "magic bullet" has almost exclusively followed a single pattern: A (usually lonely male) laboratory scientist, in search of a molecule that could cure a (usually deadly) disease, stumbles (usually accidentally) on a specific substance that is effective against that specific disease. The long and complex path from the scientist's test tube to the patient's pillbox is conspicuously absent from the story. The basic structure of the narrative, mainly produced by academic scientists and historians of the experimental sciences and medicine, should not invite ridicule. Indeed, it reflects essential tenets of the "magic bullet ideology" that, by placing the laboratory at center stage, played a crucial role in reconfiguring drug development during the first part of the twentieth century. Today the promise of the "magic bullet" looks less certain and the future of drug development somewhat more gloomy. Current historiography brings a new perspective on the ideology and offers more powerful intellectual tools to explore the process.

Unlike the standard narrative, the current historiography takes drugs to be more complex entities. They are more than molecules: they are evolving cultural productions, carrying many layers of meaning and embedded in multiple social networks.[1] New histories of drugs feature not only laboratory scientists, but also individual medical practitioners and clinicians, engineers and investors, sales representatives and pharmacists, and even patients. To put it differently, drugs are seen as products of the laboratory, the clinic, the factory, the marketplace, the law, and the media. The idea of a "drug trajectory" or "drug biography" has proven to be a powerful heuristic.[2] A biography of a drug that focused solely on its discovery would be as shallow as a biography of a person concerned exclusively with the conditions of his or her birth. Two masterly works under review (Lesch and Bud), one about the sulfa drugs and

1. See, for example, Andrea Tone and Elizabeth Siegel Watkins, eds., *Medicating Modern America: Prescription Drugs in History* (New York: NYU Press, 2007).

2. See Jean-Paul Gaudillière, "Introduction: Drug Trajectories," *Studies in History and Philosophy of Biological and Biomedical Sciences* 36 (2005): 603-11; Sjaak van der Geest, Susan Reynolds Whyte, and Anita Hardon, "The Anthropology of Pharmaceuticals: A Biographical Approach," *Annual Review of Anthropology* 25 (1996): 153–78.

the other antibiotics, exemplify this new perspective and the new insights it can foster.

No drug biography has been told more often the 1929 discovery of penicillin by Alexander Fleming and its subsequent mass production during the Second World War. More than two dozen monographs have focused on this "success" story, and the debate continues over Fleming's apparent decade-long neglect of the therapeutic potential of the penicillin substance. Robert Bud, a historian at the Science Museum in London and the author of a book on the history of biotechnology considered broadly as the use of life for industrial production, is particularly well equipped to make a contribution to this overworked topic. The originality of his approach in *Penicillin: Triumph and Tragedy* lies in his treatment of penicillin "as both a brand and a family of chemicals."[3] Even before covering, in a single chapter and standard fashion, the familiar story of Alexander Fleming, Ernest B. Chain, and Howard W. Florey, Bud describes the high hopes for wonder drugs that briefly crystallized in the first half of the twentieth century around Paul Ehrlich's Salvarsan, the sulfa drugs, and vitamins. Penicillin, becoming widely available at the end of the war, met great expectations not only for wonder drugs, but more generally for products that, after wartime hardships, would bring a better life. It was thus ideally suited to become a cultural icon of postwar modernity, or, in Bud's terminology, a "brand." He tells a fascinating story of how penicillin was "branded" by physicians, scientists, governments, the military, and the media, through independent propaganda efforts highlighting the benefits for society of modern science, industry, and government intervention. Even though Bud focuses on Britain and the United States, he also explores, in a very welcome chapter, the production of penicillin in other European countries and in China.

Where Bud's perspective on brands proves most useful is in addressing the extraordinary diffusion of penicillin in postwar consumer culture. Framed as a brand, penicillin thrived as a commodity in the marketplace. It had a profound cultural impact. For example, it shifted patients' attitudes toward therapeutic intervention, in that they increasingly considered the physician a prescriber of antibiotics, rather than a skilled practitioner of the arts of diagnosis and healing. The formidable consumption of penicillin (and other antibiotics), together with its use in large-scale animal husbandry, ironically paved the way for the brand's own demise. Although antibiotic resistance had been debated since penicillin was first used, the controversy reached a new intensity in the

3. Robert Bud, *Penicillin: Triumph and Tragedy* (Oxford: Oxford University Press, 2007), 2.

1970s and 1980s. Bud suggests that in the wake of the AIDS and BSE epidemics—neither of which is bacterial and hence neither of which can be treated by antibiotics—debates about drug resistance made ever more plausible the prospect of a world without antibiotics, the effect of the drug's very success in the marketplace. Penicillin's image as a wonder drug began to fade, even though the consumption of antibiotics had become so entrenched in consumer practices that it continued almost unaffected.

Bud has provided a powerful social and cultural history of the paradigmatic postwar wonder drug, illuminating current debates on drug resistance. As in most accounts of penicillin, however, there remains a blind spot in Bud's story toward clinical trails, fostering the illusion that drugs move smoothly from the laboratory to the market. In his account the pharmaceutical industries producing penicillin also remain something of a black box. By drawing on the literature on particular pharmaceutical companies, the author could have clarified how penicillin fit into both their research and production traditions. Indeed, the extraordinary diffusion of penicillin was predicated upon industry's ability to provide it in mass quantities. This goal attracted several companies in the immediate postwar period, but their success was often forestalled by their lack of experience and expertise in biological modes of production.

The First Miracle Drugs: How the Sulfa Drugs Transformed Medicine addresses these issues only touched upon in *Penicillin: Triumph and Tragedy*, resulting in what is perhaps the most accomplished drug biography to date. John Lesch's previous books, histories of experimental physiology in France in the nineteenth century and of the German chemical industry in the twentieth century, constitute a crucial background to his new history of the sulfa drugs.[4] As Robert Bud briefly acknowledges, penicillin was not the first miracle drug: it was preceded by the sulfa drugs, and even earlier by Salvarsan. But the sulfas were much more than a miracle drug. They inaugurated, as Lesch argues, a new "system of invention" within industry that is still in operation today. The author explores how the German chemical company I.G. Farben, under the guidance of its research manager Heinrich Hörlein, developed this innovation system in which families of chemical molecules would be screened *in vitro*, and, more importantly, *in vivo* in model animals, for therapeutic activity against a number

4. John E. Lesch, ed., *The German Chemical Industry in the Twentieth Century: Chemists and Chemistry* (Dordrecht: Kluwer Academic, 2000); John E. Lesch, *Science and Medicine in France: The Emergence of Experimental Physiology, 1790–1855* (Cambridge, MA: Harvard University Press, 1984).

of different diseases. Even though Lesch focuses on Germany, he also explores in detail how the French and British industries followed radically different paths to develop new sulfa drugs.

With the rise of National Socialism, Hörlein's project was imperiled by the Nazis' anti-Jewish laws and their endorsement of anti-vivisectionist movements. However, through a politics of accommodation with the regime, Hörlein succeeded in developing his system by bringing together I. G. Farben's traditional expertise in dye chemistry, its large-scale research facilities, and several innovative researchers, including the physician Gerhardt Domagk. Domagk's ability to see beyond disappointing *in vitro* trials and his reliance on animal models were key to the 1932 discovery of a powerful antibacterial sulfa compound, which was first marketed under the name Prontosil. This discovery earned Domagk the Nobel Prize in Physiology or Medicine in 1939.

Prontosil did not become a wonder drug overnight. Lesch shows in great detail how the specific uses of the different sulfa drugs were defined just before, and especially during, the Second World War. Here Lesch accomplishes more than he claims in his introduction, providing a unique exploration of day-to-day therapeutic implementation. Unlike most authors, he does not take the drug's efficacy as given, but as a question to be addressed. Even though clinical trials had concluded that the sulfa drugs were inefficient for treating wound infections, they were widely used for that purpose on the battlefront between 1943 and 1945. Trial under fire defined a different standard of efficacy than had clinical trials. After the war, the sulfa drugs were displaced in the news by penicillin and other antibiotics, even though the sulfas continue to be used today. But the sulfa drugs had other and perhaps more important legacies for the development of pharmaceuticals, namely, a powerful model of industrial innovation and the kindling of a persistent hope that chemistry and industrial research would produce other wonder drugs.

Lesch's exploration of this system of innovation could have benefited from a comparison with the methods of Paul Ehrlich and the chemical dye manufacturer Farbwerke Hoechst AG two decades earlier, which led to the development of Salvarsan, one of the first syphilis drugs. Indeed, in many ways, the screening approach of Hörlein seems to have been a translation of Ehrlich's approach in a large-scale industrial context. Also, Lesch, like Bud, only gives passing mention to serum (or antitoxin) therapy. Yet serum therapy was one of the most popular drug therapies in the first three decades of the century, and its development prefigured many problems encountered with the sulfa drugs and penicillin.

The only troubling aspect of Lesch's book is his treatment of Hörlein's involvement with the Nazi regime. As Lesch points out, there is no doubt that Hörlein was not a passionate Nazi supporter, but it is quite a stretch to make him a victim of unfavorable circumstances, confining him to a strategy of "accommodation and survival." The fact that Hörlein was supported by Adolf Butenandt during the Nuremberg trials should not be taken as conclusive evidence of his past actions or morals, as Lesch argues it should be. Indeed, Butenandt, we have recently learned, was a "one-man whitewashing machine," as Robert Proctor has put it, clearing some of the most horrific medical researchers, including Otmar von Verschuer (of sinister twin studies fame).[5] Describing Hörlein's values as "scientific, medical, and technical" overlooks his responsibility as a leader in a company using slave labor, producing medicines and combat gases for the military, and one whose wartime drug testing practices have not been fully explored. In short, Hörlein might have disliked the Nazis, but he served them well.

Instead of following the trajectory of a drug, as Lesch and Bud have, other historians have chosen to follow the trajectory of a medical condition, tracking the different therapeutic approaches that have been taken to deal with it. This perspective has challenged another element of the standard narrative, namely that drugs cure preexisting diseases. Indeed, the availability of drugs can also lead to the creation of new diseases, whether by transforming acute diseases into chronic ones (diabetes), unmasking diseases of advanced age (Alzheimer's), or raising incentives for defining a new disease category (hyperactivity). The two other books reviewed here (Watkins and Greene) have much to say on the co-construction of drugs and diseases.[6] For as infectious diseases receded among the most pressing medical problems in industrialized countries, the pharmaceutical industry turned toward a potentially much more profitable market, chronic diseases, of which patients would never be cured. A drug's efficacy, as Lesch has pointed out, does not result from a molecule's properties alone. By adjusting not just the (magic) bullet, but by shifting the targeted disease as well—what recent commentators have called "disease mongering"—one could produce a powerful hit between a drug and a disease.

5. Robert Koenig, "Reopening the Darkest Chapter in German Science," *Science* 288 (2000): 1576–77.

6. Among other recent examples, see Robert A. Aronowitz, *Unnatural History: Breast Cancer and American Society* (Cambridge: Cambridge University Press, 2007); and Scott H. Podolsky, *Pneumonia Before Antibiotics: Therapeutic Evolution and Evaluation in Twentieth-Century America* (Baltimore, MD: Johns Hopkins University Press, 2006).

In *The Estrogen Elixir: A History of Hormone Replacement Therapy in America,* Elizabeth Watkins, whose previous book considered the social history of the contraceptive pill, explores the medicalization of menopause and the rise and fall (and rise and fall) of estrogen replacement therapy.[7] Sexual hormones entered therapeutic practice almost immediately after their discovery in the 1890s when French physician Charles-Edouard Brown-Séquard injected himself with extracts from guinea pig testicles. Then seventy-two years old, he reported feeling rejuvenated, prompting many other men to follow his lead. In the late 1930s, other hormones such as estrogens began to be marketed on a large scale to women to treat some of the symptoms of menopause. However, the "estrogen empire" truly expanded when *long-term* hormone replacement therapy became a standard practice for post-menopausal women. In the post-war years, advocates of "estrogen from puberty to grave" succeeded in raising high expectations from hormone therapy, at a time when U.S. Food and Drug Administration (FDA) approval did not require proof of efficacy, only safety. Watkins explores how the pharmaceutical industry "sold" estrogen therapy to physicians, who in turn "sold" it to their patients, leading to the consumption of estrogen by 40% of post-menopausal women in the United States by the end of the twentieth century.

Unlike other recent authors writing on "disease mongering," Watkins does not claim to reveal a hidden conspiracy of pharmaceutical manufacturers and physicians.[8] Industry and doctors played their part, but they were joined by women patients, the popular media, and government. Even more importantly, the medicalization of menopause was also the result of deep cultural forces in American society, which increasingly equated beauty with youth, health with sexuality, and aging with an active life. Thus, when these forces defined menopause as a problem, estrogens became the answer. The rise of long-term estrogen replacement therapy, Watkins argues, came about predominantly because of the changing meaning of menopause in the twentieth century.

In 1975 an observed association between estrogen and endometrial cancer damaged the reputation of estrogen therapy, predictably leading to controversies about clinical trial methodologies. At the same time, feminist groups, trying to reclaim expertise about the female body, criticized the excessive

7. Elizabeth Siegel Watkins, *On the Pill: A Social History of Oral Contraceptives, 1950–1970* (Baltimore, MD: Johns Hopkins University, 1998).

8. See, for example, Christopher Lane, *Shyness: How Normal Behavior Became a Sickness* (New Haven, CT: Yale University Press, 2007).

medicalization of menopause. In that tense political and scientific context, the FDA went so far as to mandate *patient* labeling for estrogens, instead of the usual physician labeling. By 1980, estrogen prescriptions had dropped by 50%. Another source of criticism, not explored in the book, came from animal rights groups. These groups publicized the fact that Premarin, the best-selling estrogen, was produced from the urine of pregnant mares, whose foals, once born, would likely end up in the slaughterhouse.

A fascinating aspect of Watkins's story is how drugs can be rebranded in the face of falling sales. After years of decline, estrogen therapy rose to new heights when it was repackaged as a preventive drug against osteoporosis and heart diseases. In this radically new therapeutic perspective, the drug was not meant to cure, but to reduce risks. In 1992 Premarin became the most frequently prescribed drug in the United States. But one decade later, when a multi-million-dollar, federally funded clinical trial pointed to a number of increased health risks from estrogen therapy and questioned its overall benefits, estrogen therapy again fell in disrepute.

The story that Watkins tells, using mainly published sources such as newspapers, magazines, and medical journals, shows how much the history of drugs benefits from being placed in the context of the cultural history of particular conditions and diseases. The efficacy of a drug, far from being an intrinsic property, is a relationship between two flexible entities, a drug and a human condition. From Watkins's history, it seems that cultural forces and randomized clinical trials were the main determinants of estrogen therapy's fate. One may wonder if, in her attempt to shy away from conspiracy theories, Watkins plays down the importance of the pharmaceutical industry. Had she looked into (and been granted permission to access) the archives of Ayerst, one of the main producers of estrogens, and not just the advertisements they sponsored, she would perhaps have reached a slightly different conclusion. Indeed, the leveling of the information field between patients and physicians, which Watkins sees as characteristic of the late twentieth century and as resulting partly from the pharmaceutical industry's willingness to disclose potential risks more openly, was partially due to the industry's fear of litigation, an issue which is conspicuously absent from the book.

The physician and historian of medicine Jeremy A. Greene also explores "condition branding" in his *Prescribing by Numbers: Drugs and the Definition of Diseases*. In a sophisticated and compelling account, Greene explains how numerical values of physiological parameters became the basis for adjudicating between the normal and the pathological in the second half of the twentieth

century. Using extensive FDA and pharmaceutical industry archives, Greene follows the history of three drugs: Diuril for hypertension, Orinase for diabetes, and Mevacor for cholesterol. In so doing, he succeeds in making a much broader argument than can be found in studies based on a single drug or disease. Greene shows how a quantifying culture in medicine produced a new kind of patient on a massive scale, namely, the patient who is symptomless but yet at risk. In a nutshell, the narrower the numerical interval for a normal physiological value (be it of blood pressure or blood sugar or cholesterol or so on), the larger the population that is defined as having a pathological condition or being at risk. As with the earlier concept of a healthy disease carrier, from Typhoid Mary to the genetic heterozygote, this new form of patienthood has brought the medicalization of previously healthy individuals to an unprecedented scale. Unsurprisingly, this process has been closely linked to the availability of pharmaceutical drugs, and thus to the production of potential consumers.

Greene provides a fascinating account of pharmaceutical marketing and the complex relationships between physicians and pharmaceutical companies. However, like Watkins, he does not describe the medicalization of risk and chronic diseases as resulting exclusively from the aggressive marketing strategies of Big Pharma, even though the latter, together with other market forces, did play a major role. By taking into account the role of patient organizations, insurance companies, malpractice litigation, and other factors, Greene offers a much richer narrative of the redefinition of the normal and the pathological in the late twentieth century. Most importantly, the rise of chronic disease has resulted from the production of specific forms of biomedical knowledge in partnerships among industry, academia, and government. This does not necessarily involve "bad science" or the selling-out of academic science to corporate interests, but, more subtly, the reframing of the research agenda around questions that serve, *at the same time*, commercial, scientific, and public health interests.

It would be hard not to notice that the new historiography of drugs has become an exceptionally vibrant and innovative field, as the four examples reviewed here clearly attest. And the field can naturally be extended to include a third approach, not represented among the books under review, focusing on a particular pharmaceutical company.[9] This fecundity has given rise to a very

9. Most such volumes have either been commissioned by companies or written by independent scholars hampered by limited archival access. The genre has thus usually not yet proven as successful as studies of drugs or diseases. For a recent example to the contrary see Roy Church and E. M. Tansey, *Burroughs Wellcome & Co.: Knowledge, Trust, Profit, and the Transformation of the British Pharmaceutical Industry, 1880–1940* (Lancaster, Eng: Crucible Books, 2007).

welcome side effect, namely, a cure to some of the divisions among the history of science, medicine, and technology. One can only conjecture as to some of the directions in which a reunified field might evolve. So far, the social and cultural history of drugs has remained surprisingly disconnected from the literature produced by economic and business historians. From the macro perspective in Alfred D. Chandler's *Shaping the Industrial Century* to the more micro story in Louis Galambos and Jane Eliot Sewell's *Networks of Innovation*,[10] there seems to be some room to inscribe particular modes of knowledge production within the historical development of new visions of industrial production and the market forces that structure them. Drug research can then be understood as resulting from different "ways of knowing" connected to different "ways of producing," as John Pickstone has suggested more generally for the history of science, technology, and medicine.[11]

Along this line, one wonders if the history of drugs would not benefit from being brought under a larger heading than those of individual drugs or pathologies, or, for that matter, companies. For example, even though the sulfa drugs and penicillin were both used as antibacterial agents, the sulfas probably had more in common with vitamins, and penicillin with vaccines, than they did with each other. The actors' categories of "biologicals" (or "biologics") and "chemicals" brought together different drugs that presented similar production challenges, disciplinary commitments, regulatory frameworks, appropriation possibilities, and cultural currencies. A perspective that considered such categories would help us to draw a larger map of the therapeutic revolution in which drugs have figured so prominently.

10. Alfred D. Chandler, Jr., *Shaping the Industrial Century: The Remarkable Story of the Evolution of the Modern Chemical and Pharmaceutical Industries* (Cambridge, MA: Harvard University Press, 2005); Louis Galambos and Jane Eliot Sewell, *Networks of Innovation: Vaccine Development at Merck, Sharp & Dohme, and Mulford, 1895-1995* (Cambridge: Cambridge University Press, 1995).

11. John V. Pickstone, "Working Knowledges before and after Circa 1800: Practices and Disciplines in the History of Science, Technology and Medicine" *Isis* 98 (2007): 489–516.