The First Miracle Drugs: How the Sulfa Drugs Transformed Medicine

JOHN E. LESCH

OXFORD UNIVERSITY PRESS
The First Miracle Drugs
This page intentionally left blank
THE FIRST MIRACLE DRUGS

How the Sulfa Drugs Transformed Medicine

JOHN E. LESCH
This page intentionally left blank
We live in an age of powerful medicinal drugs. Antibiotics cure or prevent bacterial infections, diuretics and other medicines help to control hypertension, antiretrovirals add years to the lives of those infected with HIV. The list of substances that cure or palliate our ills is very long and getting longer every year. This book is one historian’s attempt to understand how we arrived at such a place, which is unprecedented in the long history of medicine and humanity before the twentieth century. I have concluded that the answer lies in the industrialization of science and medicine, and that within this historical process the introduction of the sulfa drugs in the 1930s was the event that did most to set us on our present course.

My path to this conclusion was not a direct one. This book had its origins in reflections on the relationships of industrialization and science that began in graduate school with my reading of Jerome R. Ravetz’s *Scientific Knowledge and Its Social Problems.* What did it mean to say that science became industrialized, I wondered, and what were the ramifications and limitations of such a line of analysis? Joined to my prior interest in the relationships of the laboratory sciences and medicine, such questions drew me eventually to the history of medicinal drugs and the pharmaceutical industry. I chose to work on the sulfa drugs because their study promised to allow exploration of issues surrounding industrialization of science and medicine, because their importance seemed out of all proportion to the slight attention they had received in the historical literature, and because it was clear from the very beginning of the project that the crucial role played by research in several national settings would permit, indeed would require, comparative analysis and study of transnational connections in medicine and science. As I moved further into the research and writing, the pivotal role of the sulfa drugs in initiating the modern era of medicinal drugs emerged with increasing clarity.
Little did I know what I was getting into. I am an admirer and sometime reader of Charles Dickens, but never thought of myself as a Dickensian character until I read *David Copperfield* and discovered Dr. Strong. Headmaster of a school that David attends, Dr. Strong works at compiling a dictionary of roots—not, as David at first thinks, of the botanical kind, but rather of the etymological variety. What caught my eye was not the nature of the project, but the pace at which it was prosecuted. Taking note of this, one of Dr. Strong’s students does a simple calculation and finds that his dictionary will likely be completed in one thousand six hundred and forty-nine years. While I suspect that, from time to time colleagues, family and friends have performed similar calculations on my book, I am glad to report that it has come in substantially ahead of the figure projected for Dr. Strong.

In the course of this work, I have accumulated many debts (another Dickensian motif?) that I can only begin to acknowledge here. Funding for research, and for the invaluable leaves from teaching that make it possible, has come at different times from the National Science Foundation (SES 81-11985 and SES-8409848), the National Institutes of Health (NIH-R01 LM04231), the John Simon Guggenheim Memorial Foundation, and, on two occasions, University of California–Berkeley Humanities Research Fellowships. I have also benefited from research assistantship support from the Center for German and European Studies at UC Berkeley and from numerous small grants from the UC Berkeley Academic Senate’s Committee on Research.

Parts of this book have been published in different form. I am glad to have this occasion to thank the editors Seymour H. Mauskopf, *Chemical Sciences in the Modern World* (University of Pennsylvania Press, 1993), and Gregory J. Higby and Elaine C. Stroud, *The Inside Story of Medicines: A Symposium* (American Institute of the History of Pharmacy, 1997), for invitations to the conferences that gave rise to these books and for their help in bringing my contributions to publication.

This book would not exist without the resources of numerous archives and libraries and the skills and generosity of their staffs. These include, more or less in order of their appearance in the notes, the Alan Mason Chesney Medical Archives of the Johns Hopkins Medical Institutions, with special thanks to Nancy McCall; the Bayer Archive in Leverkusen, Germany, where I was assisted during my visit by Peter Göb, and subsequently by Michael Pohlenz; the Nobel Archives in Stockholm; the Hoover Institution Library in Stanford; and the Archives of the Institut Pasteur, Paris. In London, Malcolm Goodson and Robert J. Moore facilitated my research at the Medical Research Council Archives. At the Royal Society Archives, I was helped by Mary Sampson and Sandra Cumming; at the Wellcome Institute for the History of Medicine, by William F. Bynum; and at the Contemporary Scientific Archives Centres in London and Oxford, by J.G.A. Sheppard and by Margaret Gowing and J.B. Alton, respectively.

My visit to the May & Baker Archives at Rhône-Poulenc-Rorer (now Sanofi-aventis) in Dagenham, United Kingdom, was greatly facilitated by Peter J.T. Morris, who first made me aware of its collections, and by John Salmon (then of Rhône-Poulenc-Rorer), who also helped to put me in touch with individuals who had been involved in research and development on M&B 693. Jeffrey Sturchio helped
to arrange my visit to the Merck Archives in Whitehouse Station, New Jersey, where Joe Ciccone and Amber Olterzewski responded readily to my various requests for information and documents. Many people assisted my research at the National Archives in Washington, DC, among them notably John Taylor and George Wagner at the Modern Military Branch. Thanks are due also to Michael G. Rhode at the National Museum of Health and Medicine, Armed Forces Institute of Pathology, Washington, DC, for location of a photograph used in chapter 10. Finally, I am grateful to the staff of the Bodleian Library, Oxford, for their help with the Donald Devereux Woods papers.

I have depended heavily on other libraries, not for archival materials but for their rich collections of published sources and skilled and responsive staffs. Especially important for this project have been the libraries of the University of California–Berkeley, the Lane Medical Library of Stanford University, the Kalmanovitz Library of the University of California–San Francisco, and the National Library of Medicine in Bethesda, Maryland.

The Department of History of the University of California–Berkeley has been a wonderful intellectual environment in which to work, and I am grateful to a succession of chairs of the department for their steady support of this project. No less important has been the intellectual community and material support provided by UC Berkeley’s Office for History of Science and Technology. I am especially grateful to its directors, John Heilbron, Roger Hahn, and Cathryn Carson, and its excellent administrator, Diana Wear, for their assistance in a myriad of ways over the years.

Margaret Anderson, John Parascandola, John Swann, and Paula Fass read the whole manuscript of this book in its penultimate version and offered detailed and valuable comments that have made the final version better than it might have been. I have not been able to incorporate all of their suggestions, but I am grateful for their insights and, in several instances, for their corrections of errors. The faults that remain are, of course, entirely my responsibility.


My thinking on the problems and themes of this book has been developed and sharpened in countless classroom presentations and discussions, and for that I am glad to thank my students. It is something of a cliché in academia that teaching and research should benefit one another. In this case there is no doubt of the fact.

Students have contributed to this project in a more direct way, as research assistants or by helping to enter my longhand drafts on the computer. My thanks go to Jesse Berrett, Renee Coury, Ki Won Han, Marianne Miller, Julia Rechter, Jonna Van Zanten, and Alex Wellerstein. For typing and other crucial tasks, I am also
indebted to Department of History staff at different stages of the project, especially Nadine Ghammache and Sherrill Young.

Going from a manuscript to a book is in itself a process of many stages, and I am indebted to the people at Oxford University Press who have made it happen. Special thanks go to Jeffrey House, who first welcomed the manuscript; to my editor, Carrie Pedersen, who managed its progress with diplomacy, skill, and good feeling; to Regan Hofmann, who with energy and tact kept me focused on the task at hand; to my copyeditor, Trish Watson; and to Keith Faivre, who managed the book’s production.

More important than anything else has been the support of my family. My daughter Bibi and my son Charlie literally grew up with this project, and their presence has made the journey a wonderful one at every stage. In numerous conversations around the dinner table, Charlie urged me to find ways to make the book more accessible, and Bibi has inspired me with her own enthusiasm for science and medical research. Paula Fass has been there from the beginning, encouraging, admonishing, reading, and criticizing drafts and accommodating my work in many other ways in the midst of our family life and her own very busy career. We have made this trip together, and I gladly dedicate this book to her.
Contents

Introduction 3

Part I  The Industrial Origins of Prontosil

1  Beginnings 15
2  A System of Invention 40
3  Prontosil 51

Part II  The Making of the First Miracle Drugs

4  Into the Maelstrom 71
5  Accommodation and Survival 92
6  Pathways of Recognition 122
7  M&B 693 158
8  Acclaim and Expansion 184

Part III  Practice and Theory

9  At War 207
10  Trial by Fire 222
11  A Mechanism Revealed 251
12  The Sulfa Drugs and Twentieth-Century Medicine 269

Notes 293
Index 349
This page intentionally left blank
The First Miracle Drugs
Introduction

On Christmas Day 1932, the German chemical combine I.G. Farbenindustrie filed a patent application on behalf of a red dye that its medical researchers and chemists had found to have a remarkable ability to cure certain kinds of bacterial infections in mice. By the time the patent was awarded just over two years later, the dye, now called by the trade name Prontosil, had been found to have the same curative powers in humans. Announced in a brief publication in a German medical journal in February 1935 by Gerhard Domagk, the medical researcher responsible for the work, Prontosil went on the market and became available to doctors in April 1935.

In retrospect, it is clear that the introduction of Prontosil marked a turning point in the history of medicine. As the first of the compounds called sulfonamides or, more familiarly, sulfa drugs, Prontosil initiated a revolution in the therapeutics and management of bacterial infections. Within a few years, feared diseases such as streptococcal infections (including childbed fever and septicemia), pneumonia, meningitis, dysentery, gonorrhea, and urinary tract infections, were brought under a substantial measure of control by chemotherapy. The medical success of the sulfa drugs gave a powerful impetus to the expansion of the international pharmaceutical industry and of the research and development enterprise within it. The same success contributed heavily to the opening of what was widely referred to as an era of miracle drugs, with its attendant optimism and raised expectations of medicine, accelerated appearance of new medicines as a result of increased levels of research, regulatory dilemmas, and unanticipated therapeutic problems. Finally, the sulfa drugs proved extraordinarily fruitful as starting points for molecular modifications that led to new drugs or classes of drugs not only for bacterial infections (eventually including tuberculosis) but also for leprosy
(Hansen’s disease), diabetes, hyperthyroidism, gout, heart disease, and hypertension. The reach of research based on the sulfa drugs extended beyond human into veterinary medicine and even to the discovery of new herbicides.

Other writers have used the phrase “therapeutic revolution” to refer to the discontinuity in the history of medicine initiated by the introduction of the sulfa drugs. In this usage, the therapeutic revolution is a compact denotation of an aggregate of events, including rapid expansion of pharmaceutical research, development, and production, that issued a steady and, in quantitative terms, unprecedented flow of new medicines onto the market and into medical practice, a flow that has continued from the late 1930s to our own day and that has transformed the practice of medicine.¹

If the sulfa drugs were the first act of the therapeutic revolution, they were also a culminating event in a larger historical process stretching back to the 1880s, which may be called the industrialization of pharmaceutical innovation. Behind this process was the rise of a fine chemicals industry (that is, one that manufactures products such as dyes, pharmaceuticals, and photographic products) based on synthetic coal tar chemistry beginning in the 1860s, especially in Germany, and the industrialization of invention within this industry between 1880 and 1914.

For all human history until the 1880s, medicines had been derived almost exclusively from natural products, plant, animal, or mineral. Among these sources, plant extracts were by far the most important. The first great medical achievement of analytical organic chemistry in the nineteenth century was the isolation of active principles of plants, including morphine from opium and quinine from cinchona bark, and their characterization as members of a new chemical class, the alkaloids.²

With rapid development of analytical, synthetic, and structural organic chemistry in the middle decades of the nineteenth century, chemists moved beyond isolation of natural products to their synthesis. More important, they began to recognize the potential medical usefulness of organic compounds prepared in the laboratory. A crucial turning point came in the 1880s, with the realization by German chemists that certain coal tar derivatives have powerful fever- and pain-reducing properties. One of these compounds, phenacetin, introduced in 1887, was manufactured by the German fine chemicals company Bayer and found widespread use in medicine. Recognition of the pharmaceutical potential of coal tar derivatives, joined with increasing industrial connections to academic organic chemistry and legal and economic incentives for diversification, propelled companies such as Bayer, which were already in possession of extensive knowledge of coal tar chemistry through work on synthetic dyes, into pharmaceutical research. One of the important early products of the Bayer pharmaceutical laboratories, established in the 1890s, was acetylsalicylic acid, marketed in 1899 under the trade name Aspirin.³

The same decades that saw the establishment of research within the German fine chemicals industry also witnessed spectacular developments in bacteriology and the germ theory of disease. By the early 1900s, microbial parasites had been associated with more than a score of serious human and animal diseases. Synthetic
organic chemistry and the germ theory were joined in Paul Ehrlich’s program for chemotherapy, which aimed to identify compounds that would destroy infectious organisms without harming the host, and in the 1910s the German chemical industry took another major step by incorporating Ehrlich’s research program into its own pharmaceutical research effort. From 1900 through the 1920s, a variety of new medicines came out of German industrial pharmaceutical research, including barbiturates, local anesthetics such as Novocain, the sleeping sickness medicine Bayer 205 (Germanin), and the antimalarial Atabrine.4

Meanwhile, France, Britain, and the United States lagged behind in building up industrial research and development in pharmaceuticals. The 1914–1918 war shocked other countries into recognition of their dependence on Germany for imports of fine chemicals, including drugs. In the 1920s and 1930s, efforts were made in France, Britain, and the United States to develop synthetic organic chemicals manufacturing and industrial, or industry-linked, pharmaceutical research. In areas of drug innovation that were not so dependent on medicinal chemistry in the sense of molecular synthesis and molecular modification, but rather on the isolation, purification, and chemical and physiological characterization of naturally occurring compounds such as hormones and vitamins, much important work was done outside of Germany between 1900 and 1935. In many cases, the development of such research for medical and commercial purposes entailed academic–industrial cooperation and stimulated expansion of industrial–pharmaceutical research. By the late 1930s, when the sulfa drugs arrived on the scene, the beginnings of industrial pharmaceutical research and the links of such research to academic science were in place in France, Britain, and the United States, although none of the these countries could yet challenge German leadership in medicinal chemistry.5

This situation was transformed first by the response of French, British, and U.S. industry to Prontosil and its effective component, sulfanilamide, and then by a new World War. The sulfa drugs helped to spark an expansion of pharmaceutical production and research and development that began before World War II and that was accelerated by it. The war removed German pharmaceutical manufacturing and research from serious competition, at least until postwar recovery began. The result was the emergence after the war of a larger and more truly international pharmaceutical industry in which the United States had replaced Germany in a leading position.6

The sulfa drugs therefore stand at a pivotal moment in the history of twentieth-century medicine. They are at once the culminating event of the first major phase of the industrialization of pharmaceutical innovation, and the initial event of the second great phase of that process, the therapeutic revolution that continues in our time.

Those who witnessed the introduction of the sulfa drugs into medicine recognized that a major break with the past was under way. One of the earliest attempts at an appraisal was made by F. Sherwood Taylor, whose book *The Conquest of Bacteria: From Salvarsan to Sulphapyridine* appeared during the war in 1942. Writing for a lay audience, Taylor presented the sulfa drugs as the triumphal outcome of long research based on Ehrlich’s program and ultimately on the bacteriology and synthetic organic chemistry of the late nineteenth century. Looking to the future,
he called for more substantial public support of research in chemotherapy. Also written for a general audience, although in this case by a physician, Iago Galdston’s *Behind the Sulfa Drugs: A Short History of Chemotherapy* (1943) presented the sulfa drugs as the “crowning achievement” of curative medicine, with antecedents much like those described by Taylor.7

Neither Taylor nor Galdston mentioned penicillin, which was the object of a crash wartime Anglo-American development project when their books appeared. By the time that American medical researcher Boris Sokoloff published *The Miracle Drugs* in 1949, again for a general audience, the sense of dramatic change persisted, but its content had been reshaped to take into account penicillin and other antibiotics, substances with powerful antibacterial action that, unlike the sulfa drugs, were derived in the first instance from living organisms. Sulfa drugs still counted as miracle drugs in Sokoloff’s account, but his book allotted them a relatively small proportion of its pages and included information on toxicity and bacterial resistance.8

For the most part, those who wrote on the sulfa drugs in the 1930s and 1940s, including Taylor, Galdston, and Sokoloff, focused on their importance as antibacterial agents and their role in reviving interest in chemotherapy. As penicillin and other antibiotics displaced sulfa drugs from news headlines and medical practice, popular awareness of the historical role of the sulfa drugs in initiating a new era in medicine receded. Nevertheless, by the late 1950s and 1960s, it was clear to some observers more intimately familiar with pharmaceutical research that the importance of the sulfa drugs extended well beyond the chemotherapy of bacterial infections. By the 1960s, chemists and medical researchers, often working in industrial laboratories enlarged or created in part because of the earlier success of the sulfa drugs and exploiting knowledge or insights gained in research on the sulfa drugs, had employed molecular modification to develop new drugs or classes of drugs for a variety of diseases and conditions most of which were not infectious. Among the most articulate commentators on these developments was Max Tishler, who served as director of the Merck, Sharp & Dohme Laboratories from 1957 to 1969 and president of the American Chemical Society in 1972, and who reflected on the recent history of medicinal chemistry in a series of papers and talks in the late 1950s and 1960s.9

By the 1980s, perceptive writers on the history of medicinal drugs began to describe the sulfa drugs as the leading edge of what was increasingly seen as a wider therapeutic revolution embracing bacterial chemotherapy, antibiotics, and the many other new kinds of drugs that followed, but also rapid expansion of pharmaceutical production and research, new precision manufacturing methods, and new drug evaluation and regulatory problems.10

In 1988, Daniel Bovet, a Nobel laureate in Physiology or Medicine for work on synthetic curares and antiallergy medicines, and himself a participant in a crucial early episode in the development of the sulfa drugs, published *Une chimie qui guérit: histoire de la découverte des sulfamides* (*A Healing Chemistry: History of the Discovery of the Sulfonamides*). This wide-ranging, informative, and often engaging study did justice to the international character of the sulfa drugs story, with discussions of developments in France, Germany, Britain, the United States,