

BOOK REVIEWS

Drug Discovery—A History. Walter Sneader, John Wiley, New York, 2005, Cloth, 468 pp, \$65.

I count myself fortunate to own copies of Walter Sneader's books on drug discovery: *The Evolution of Modern Medicines* (1985), *Drug Prototypes and Their Exploitation* (1996) and *Drug Discovery – A History* (2005). While it is true that each book generally addresses the topic of drug discovery with significant overlap in the material covered, it also is true that the most recent work is much more than a third edition of an existing book. As the title promises, the focus is on history. Because chemical structures are included with the text, I found the content of this book to be uniquely satisfying to a chemist interested in history. The material in this book is organized by the source of drug prototypes rather than chronological order of discovery or therapeutic indication. This aspect of the work allows one to connect the flow of information from one type of therapy to another based on medicinal chemistry knowledge and occasionally exploitation of unexpected results. To get the full value from this scheme, one must use the index to connect all of the pieces of some stories. For example, the discovery of aspirin and NSAIDs does not appear in the same section even though the drug mechanism of action and the structures are related.

Part 1 – Legacy of the Past. In this part of the book, Professor Sneader leads us through the early evolution of medical thought and practice and ties this subject to the discovery of minerals and plant substances that appeared to have therapeutic benefit. The section on

mercury is particularly interesting. Study of this substance eventually led to the discovery of arsphenamine, an organomercurial used to treat syphilis and much later stimulated the discovery of the potent diuretic ethacrynic acid. This and other interesting stories set forth in this section help us to understand the evolutionary nature of drug discovery from a historical perspective.

Part 2 – Drugs from Naturally Occurring Prototypes. In this section of the book Sneader covers three important topics in the history of drug discovery. Plants, hormones, and microorganisms proved to be rich sources of new medicines after advances in science permitted isolation and purification of active components. Here we are provided with the historical background that led to initial discovery of useful activity, followed by isolation and purification of the active substance, structure determination, total synthesis, and in some cases manufacture of the drug. Morphine and quinine serve as clear examples of the complete process. Next we are informed about the discovery of hormones beginning with the era of organotherapy when people were exposed to various glandular extracts of uncertain composition in hopes of achieving some therapeutic benefit. As was the case with plant extracts, isolation and identification of physiologically active substances were key to progress toward better defined therapy. Discovery of biogenic amines, acetylcholine, and steroids provide informative examples of how these discoveries evolved into important new drugs. This section of the book concludes with a discussion on the discovery of antibiotics produced by microorganisms.

Part 3 – Synthetic Drugs. The discovery of aspirin, hypnotics, and barbiturates provides us with interesting insight into the discovery of early drugs derived from synthesis and their contribution to the beginnings of the modern pharmaceutical industry. Set forth here also is the remarkable course of events that led from study of organic dyes to stain tissue and bacteria to discovery of anti-infective sulfonamides, carbonic anhydrase inhibitors, thiazide diuretics, alternatives to quinine for treatment and suppression of malaria, and oral hypoglycemic agents for managing diabetes. Here Sneader's organizational scheme for the book provides value to those trying to understand how one discovery can lead to another in unanticipated ways.

In the case of adrenaline, study of analogs led to agonists and antagonists. The search for a histamine antagonist was pursued by screening rather than design. This process was successful and gave us an array of therapeutically useful antihistamines. Surprisingly, this

search also produced compounds that were later shown to be dopamine antagonists as well as histamine antagonists. One of these, chlorpromazine, opened the door to modern drug therapy for a variety of mental diseases. This remarkable story is one of the highlights of this book because it illustrates how closely related structures can have different biological properties. Other stories in which screening for biological activity was a critical part of an important discovery (NSAIDs, Angiotensin-II antagonists, etc.) are included in this section of the book.

I found *Drug Discovery – A History* to be an entertaining as well as an educationally enlightening read. For example, on page 360 Sneader claims that the often told story about the role of Hofmann's father in the discovery of aspirin was not as important as other events. While organization by drug prototype does require the reader to use the index carefully to put many of the stories into proper perspective, the process works. *Dr. Paul S. Anderson, 1233 Buttonwood Drive, Landsdale, PA 19446.*

JBC Classics and Reflections, American Society for Biochemistry and Molecular Biology, Bethesda, MD, 2006(?), 766 pp, ISBN 1-893571-08-4, Available from: P. Roux, ASBMB, 9650 Rockville Pike, Bethesda, MD 20814-3996, \$15 + \$8 shipping.

This is a compendium published to celebrate the centenary of the *Journal of Biological Chemistry (JBC)*, whose first volume appeared in 1905. Each paper has already appeared in the *JBC* in some form. It is divided into two parts. The first part contains "Reflections" by fifty-four eminent biochemists written especially for the *JBC*. The second part ("Classics") is a set of 110 short essays by editors of the *JBC* on some important papers that appeared in the journal during its first hundred years.

Biochemists of my acquaintance know little of the history of their subject. It is good here to refer to a recent article by Jensen (1). Courses in the history of science are rare and where they exist are seldom required for any degree program. In biochemistry particularly (and

especially in the molecular biology community) there is a widespread sense that the literature older than ten years is useless. This is less true in organic chemistry where a good synthesis is good forever, although perhaps not since a reading knowledge of German, in which so much of the older literature exists, is also seldom required these days. But these are arguments dealing with immediate utility. Perhaps it is more important to have one's mind stretched a bit by contemplation of how experiments were done when our current instrumentation was not available. It could be argued that a greater effort of the mind was required in those days and certainly more work.

This volume could easily be used as a textbook for a course in the History of Biochemistry. Every important area is there. It could be used in conjunction with a standard textbook in General Biochemistry as a starting point for students' essays on the history of particular areas, or it might be used in a separate course in which all of the important areas and their interrelationships are included. The volume contains many references and illustrations.

The “Reflections” are similar to the autobiographical accounts that appear in *Annual Reviews of Biochemistry* and are just as varied. Some are detailed accounts of research. These are the ones that would serve well for inquiries into the development of particular lines of research and so especially suitable for the pedagogical purposes already mentioned. Others have a broader appeal. Among these are (I cannot give page references, see below): Reichard’s sad tale of why Avery never got the Nobel prize, Mildred Cohn’s heroic instrumental work with du Vigneaud, Horecker’s charming account of his discovery of sedoheptulose [I can supply the source of the verse that he quotes (2)], Roseman’s footnotes, Westheimer on compartmentalization, the humility of H. L. Kornberg, Lehman’s rejection by the JBC, Klotz’s first page, Sela and serendipity, Korn and hard work, and Schachman for many reasons. Throughout, one is inspired by the joy that these people felt in their work and by the inspiration that all transmitted to their students.

There is less meat in the “Classics” section, but every one is worth reading. Note that, unlike the “Reflections,” the “Classics” have not previously appeared in print; they were only available on line. This has had the reasonable consequence that supplementary material such as facsimiles of the original papers and the like are still only available on line. I also note that many of these articles cite more than one paper, so that more than 110 are discussed. Each one is coupled with some often fascinating biographical material. Many, but not all (why not?), include a picture of the eminent person.

There is so much that is excellent in this volume, but it could be improved. Perhaps these remarks will affect the second volume and even provoke a revised 2nd edition of the first. A lack of proof reading has resulted in the printing of a picture of Wyman’s grandfather rather than Wyman on p 77 of “Classics.” Kornberg’s picture on p 239 of “Classics” also masquerades as Ochoa’s on p 139. These errors have been recently corrected in an erra-

tum sheet, but many uncorrected copies are in existence. The “Classics” section is properly paginated. However, no one took the trouble to repaginate the “Reflections.” The only page numbers are the originals from the *JBC* so that, for example, Kornberg’s fine article, “Remembering our Teachers,” is printed as it appeared in the Jan. 5, 2001 issue with pages 3-11. This is immediately followed by Fridovich’s article from August of that year with the pagination 28,629-28,636. This makes the first 492 pages difficult to navigate. In any revision, the editors should consider ordering the “Reflections” according to the birth date of the author rather than according to the date that the articles appeared in the *JBC*. Reichard’s intriguing account of why Avery never received the Nobel prize sometimes names him “Osvald” and sometimes, properly, “Oswald.” Where were the proofreaders? In mitigation of these criticisms, let me say that, at \$23 for nearly 800 pages (on glossy paper), the collection is a tremendous bargain, but would an index—at least a name index—have increased the price so much? An index should be a priority in any future volume of the set.

It is hard to say without an index, but my impression is that Harland Wood is the most admired scientist in this collection. His picture appears many times and his praises abound. Arthur Kornberg is close behind.

I am grateful to Prof. V. Gopalan for his comments. E. J. Behrman, Department of Biochemistry, The Ohio State University, Columbus, OH 43210.

REFERENCES

1. W. B. Jensen, “Textbooks and the Future of the History of Chemistry as an Academic Discipline,” *Bull. Hist. Chem.*, **2006**, 31, 1-8.
2. H. Baum, *The Biochemists’ Songbook*, Taylor & Francis, London, 2nd ed., 1995.

Adolf Butenandt und die Kaiser-Wilhelm-Gesellschaft: Wissenschaft, Industrie, und Politik im "Dritten Reich." Wolfgang Schieder and Achim Trunk, Ed., Wallstein Verlag, Göttingen, 2004, 450 pp, €34.

On March 1, 1943, so Werner Heisenberg relates in his memoirs, he and Adolf Butenandt attended a lecture in the air ministry in the center of Berlin on the physiological effects of modern bombs. At the lecture's end air raid alarms sounded and the participants rushed to the shelters. They barely escaped with their lives. The two Nobel laureates made their way on foot from the center of Berlin to the distant suburbs where their homes and research centers were located. They climbed over rubble, walked around burning beams, stepped onto phosphorus which set their shoes on fire till they extinguished them in puddles. And on that walk they sketched out how Germany could make the transition from irrationality to rationality, from national defeat to peace, with Heisenberg and Butenandt guiding the process. Their emphases: the unbiased rationality of science free of politics, and a focus on Germany's youth. Heisenberg was head of the German atom-bomb project, while Butenandt, much less well known, was a pioneer in research on sex hormones.

That episode is one of many, though few as stark, giving the reader of *Adolf Butenandt und die Kaiser-Wilhelm-Gesellschaft* an insight into life within Germany during the Nazi era. I had worked previously on studies of two other Nobel Laureates, Fritz Haber and Heinrich Wieland, the former, of Jewish background, forced to flee Germany, while Wieland, a non-Jew, managed to keep many part-Jewish chemists in his research team. He never gave the Nazi salute.

How should one evaluate Butenandt? He was awarded the Nobel Prize in 1939, but the Nazi regime refused to let him accept it. This hurt. He was never an ardent Nazi. On the other hand he had not warmed to the Weimar Republic. He was no democrat. He was a patriot. He was delighted with Hitler's successes as long as they were achieved peacefully, but his feelings changed markedly when war began and he foresaw the suffering it would entail. By joining the party he became director of the Kaiser Wilhelm Institute of Biochemistry in Dahlem on the edge of Berlin, one of the research institutes of the national Kaiser Wilhelm Gesellschaft (hereafter KWG). He retained this prestigious position after the war. During 1948-49 the various KWG institutes agreed to join a new organization, the Max Planck Ge-

sellschaft (MPG), Butenandt playing a not insignificant role in holding all the constituent parts together. He was elected MPG's president in 1960 and retained the position for twelve years, after which he was named MPG's honorary president. He died in 1995.

Hitler and the Nazis had assumed power in 1933. Two years later Butenandt visited colleagues and research centers in the U.S and was offered a professorship at Harvard, which he declined. The Rockefeller Foundation, which almost completely terminated support of German research after 1933, continued to support Butenandt, so highly was he regarded as well as the quality of his research.

When the *Bulletin* editor asked me to review a Butenandt biography, I was reluctant. On seeing the book, however, I quickly realized that it could be fascinating. Butenandt never admitted to any misdeeds during his many years of holding a leading position in Nazi Germany. That raised questions and those questions are the focus of this book. How could he, given his position and scientific stature, not be involved in Nazi-instigated biochemical studies involving humans and human materials from concentration camp inmates and victims? Accusations have been made by a number of authors though none of them, according to this book, by trained historians of science. One major problem was the mysterious disappearance of Butenandt's locked, private secret file. That was sufficient to cause suspicions.

The MPG cannot possibly mount investigations into the Nazi past of all its members, even all its illustrious members. But Butenandt, as head of the Dahlem institute and later of the MPG, warranted special consideration. A careful investigation into his role in the Nazi era would reflect for good or ill on the MPG itself. Accordingly, the MPG gathered an international group of historians of science (U.S., British, French, German, and Austrian) to investigate every aspect of his life and work from the Nazi assumption of power in 1933 until the KWG became the MPG.

One of the two leaders of the project, Wolfgang Schieder, did cover Butenandt's life during the Weimar Republic by looking for the influences—parental, social, political, and scientific—that helped make him the man he was. Butenandt's anti-Semitism apparently was of the conventional kind; he was never a rabid anti-Semite and valued his friendship with Otto Warburg and Otto Meyerhof. His directorship of the biochemistry institute became possible through the forced departure of Carl Neuberg, but after the war Butenandt took steps—unsuc-

cessful as it turned out—to make possible Neberg's return. He was, according to one author, neither a monster nor a hero of science but a rather typical example of a competent scientist in the Nazi era. One made compromises to survive.

What about those secret archives? They were confiscated immediately after the end of World War II by the French occupation authorities, because Butenandt had managed to move his institute from battered Berlin to the almost untouched Tübingen in the French zone. The French, we read, were less interested than the other allies in identifying war criminals, but like the others they were intensely interested in scientific and technical information they could use. They even helped Butenandt reestablish himself in Tübingen. Appeals to the French to release the files, or at least to allow scholars to examine them, were turned down or ignored, even when Butenandt himself appealed for them in the 1980s. Thus the eleven historians had to rely on other sources as well as interviews. The sources included very extensive archives at the MPG as well as weekly letters Butenandt wrote to his parents from 1921 to 1959. No evidence has surfaced incriminating Butenandt in concentration camp experiments, though he was friends with some scientists who were involved. He even was a character witness for some and remained friends with them.

There are chapters here on German research on race differences, biochemical and otherwise, including studies looking for race-specific proteins. We should not forget that the concern for racial purity was not an exclusively German phenomenon. Houston Chamberlain, who wrote a seminal work on Aryan supremacy, began as an Englishman; and concerns about miscegenation are not unheard of in our country. There is a harrowing chapter describing some of the experiments Dr. Mengele, the SS (Sturm Staffel, storm trooper) doctor and "angel of death," dreamed up and carried out at Auschwitz.

One of the problems of reviewing a collective work is how to give credit to some authors without slighting the others. Every one of these chapters is extraordinarily well and insightfully written. And the continuity of the narrative shows the effectiveness of the scheduled discussions

among the coauthors and the expert hand of the editors. But I cannot resist identifying Helga Satzinger, the author of "Adolf Butenandt, hormones and sex: ingredients of a scientific career."

Satzinger's chapter is feminist revisionism at its best. She focuses on the scientific contributions of Butenandt's wife, Erika Butenandt, whom he never listed as coauthor. Yet his letters to his parents as well as other sources reveal the extent to which Butenandt, the chemist, relied on his wife's skills and knowledge in physiology. Her contribution is not mentioned in the Butenandt section of *Nobel Laureates in Chemistry* (L. K. James, Ed.) nor in studies I have seen of women centrally involved in chemical achievements.

Butenandt tended to think hierarchically: chemistry above biology, male above female, Germany above all other countries. His institute was hierarchically organized (as was Ingold's in London when I was there) but the Dahlem Institute—unlike Ingold's—made it difficult for gifted women scientists to receive their due. Satzinger gives details.

Just as Butenandt needed his wife to do his research, so he also needed industrial cooperation and support. The detailed account of his cooperative work with Schering is an important study of academic-industrial cooperation involving a pharmaceutical company far smaller than the much studied giants Bayer and Hoechst.

After the war Butenandt revealed himself as an astute—nay brilliant—science manager, dedicated to science, willing to make the minimum compromises to preserve his institute and his research programs, all of which were too "pure" to leave him long on the list of suspected war criminals. Strangely, he apparently never faced the question whether there might be ethical limits to "pure" research. He was a consummate science-politician reestablishing and nurturing international contacts and revitalizing German science.

A final, intriguing footnote: the U.S., according to one author, did more to control every aspect of science during World War II than did Germany under the Nazis. *Otto Theodor Benfey, Greensboro, NC.*

Chemistry, Pharmacy, and Revolution in France, 1777-1809. Jonathan Simon, Ashgate, Aldershot, 2005; hardcover, vi + 189 pp., ISBN 0 7546 5044 8.

In this stimulating and important book, Simon explores the fate of pharmacy and its relationship with chemistry during the period indicated in his title. The period embraced two famous revolutions—the chemical revolution and the French revolution—and these events form both background and foreground for his story. His treatment explores the internal dynamics and linked trajectories of pharmacy and chemistry in France, as well as their social, political, and institutional histories.

Simon begins his story with the founding in 1777 of the Collège de pharmacie de Paris, essentially a new guild that separated French apothecaries from the épiciers (spice-merchants) with whom they had hitherto been combined. Soon thereafter the Collège was authorized to offer public courses on pharmacy, previously a right only of the Paris Faculty of Medicine. The French revolution shattered this arrangement, as it did so much else. In 1803 a new law, engineered by Antoine-François de Fourcroy, abolished the private guild structure entirely, brought pharmacy within a system of state administration and education, and created the basis for a modern pharmaceutical profession in France. From this point on, pharmacists would be trained in a series of state-run pharmaceutical schools (the Paris Collège de pharmacie, renamed Ecole de pharmacie, continuing its existence as one of these).

Already in 1797 Fourcroy, as a prominent citizen of the French Republic, had openly placed his cards on the table. It was not enough to modernize pharmaceutical institutions in accordance with the recent revolutionary political events, he wrote. Another revolution had also taken place, the one in the science of chemistry. Chemistry, closely tied with pharmacy since its origins, had

now become a true independent science, as a consequence of the transformations effected by Lavoisier's theories. Fourcroy argued that pharmacy must therefore henceforth accept a subsidiary position: pharmacists must study chemistry to become competent in their craft, not the reverse, and they must reveal all their proprietary secrets of the guild—modeling themselves after the openness of a real science. In Simon's phrase, French pharmacy "found itself suddenly subjugated to an independent discipline that seemed to appear from nowhere" (p 47). Simon concludes the chronology by discussing a brash 1809 proclamation to the Paris Society of Pharmacy by a modernist clique within the Society. These men proclaimed that "observer-pharmacists" (those properly inducted into the new science of chemistry) could no longer associate with "manipulators," mere empirical artisans. The divorce was complete, and there was no question which field dominated.

This is the outline of the story, but the book is considerably richer than that. Simon's fundamental thesis is that we cannot properly understand (and we have not hitherto properly understood) the history of French chemistry in this period without a fuller appreciation of the history of pharmacy. His argument is compelling. Most historians of eighteenth-century chemistry, Simon points out, have focused too exclusively on theory, neglecting the close connections between chemistry and its practical applications—pharmacy in the first line. Simon is, of course, not the only contemporary historian of chemistry to focus anew on the artisanal side of chemistry and early modern chemistry; one thinks of the outstanding work of Pamela Smith and Ursula Klein, for example. But for all interested in this subject, or in a refreshing new view of the chemical revolution itself, this book is highly recommended reading. *Alan Rocke, Case Western Reserve University.*