BOOKS: MOLECULAR BIOLOGY

# Proving Watson-Crickery, Napkin by Napkin

**Nathaniel Comfort**

**Meselson, Stahl, and the Replication of DNA**
**A History of "The Most Beautiful Experiment in Biology"**
*by Frederic Lawrence Holmes*

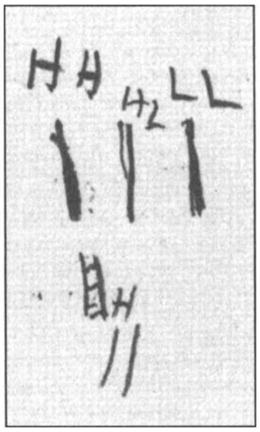
Yale University Press, New Haven, CT, 2001. 515 pp. $40, £30. ISBN 0-300-08540-0.

Beauty is not the same thing to a scientist as to everyone else. A beautiful experiment is original in approach, dazzling in technique, unambiguous in interpretation, and indisputable in its importance. Unlike a handsome profile or a snow-capped range, appreciation of the Meselson-Stahl experiment, which the biologist John Cairns called "the most beautiful experiment in biology," requires a bit of explanation.

Near the end of their classic paper describing the DNA double helix, James Watson and Francis Crick wrote, "It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material" (*1*). They saw that because each nucleotide subunit pairs with only one other type of nucleotide, each strand of the DNA molecule could serve as a template for the synthesis of a new strand. If that was correct, after replication each daughter double helix would consist of one parental strand and one new strand. This process, termed semi-conservative replication, is not the only way copying could work. Replication might have turned out to be conservative, with both daughter strands synthesized de novo, or dispersive, with daughter strands composed of alternating fragments of the parent strands and newly formed segments. For a time, each mechanism had its proponents. Then, in 1957, Matthew Meselson and Franklin Stahl proved that Watson and Crick were right.

Meselson and Stahl's experiment was—and remains—elegant. Bacteria are grown for many generations in a medium containing a heavy isotope of nitrogen, $^{15}N$, which they incorporate into their DNA. This leads to both strands of the parental DNA being heavy with $^{15}N$ (HH in shorthand). These bacteria are transferred into medium containing ordinary nitrogen, $^{14}N$, and allowed to divide. After one round of replication, daughter DNA consists of one heavy and one light chain (HL). Successive subsequent generations contain an increasingly large fraction of DNA that is LL. DNA is extracted at intervals, and the samples are centrifuged in a density gradient. Spun with forces that, as Horace Judson wrote, would "flatten an elephant into an oil slick" (*2*), DNA collects in discrete regions of the gradient, according to its specific density. In the simplest version of the experiment, one obtains three bands: HH, HL, and LL.

Frederic Lawrence Holmes has assembled a meticulous, masterly history in *Meselson, Stahl, and the Replication of DNA*. Holmes, a Yale professor whose previous work includes scientific biographies of Antoine Lavoisier and the biochemist Hans Krebs, focuses on what he calls the fine structure of science. He pores over laboratory notebooks, correspondence, and sketches on coffee-stained napkins, to reconstruct a day-by-day, sometimes hour-by-hour account of laboratory practice. For this study, as in his research on Krebs, he spent hundreds of hours with the principals, plumbing them for recollections and quizzing them on the intimate details of their experimental method. His account is not light reading; the mountain of detail often obscures the thread of the story. But so it is in science. The persistent reader is rewarded with the sensation of beginning to think like a pioneering and brilliant molecular biologist.



**Trace of an explanation.** Meselson sketched these three bands on the back of a log sheet for one of the centrifuge runs from the first $^{15}N$ transfer experiment with *E. coli.*



The book contains few revelations but scores of illuminating details. Holmes exposes no lapses of integrity, as Gerald Geison did in *The Private Science of Louis Pasteur* (*3*). Nor does he present facts that will require the rewriting of biology textbooks. He shows that the germ of the experiment came from Max Delbrück—father, muse, and drill-sergeant to the first generation of molecular biologists. Delbrück's devotion to dispersive replication later made him the most voluble critic of the semi-conservative model. Though Stahl's contributions were numerous and critical, Meselson was the team's driving force. Together they developed cesium chloride density-gradient centrifugation, which became a defining technique of 1960s molecular biology. Initially, they planned to carry out the experiment using bacteriophage instead of bacteria. In addition, their first approach to creating heavier DNA strands used 5-bromouracil, which can substitute for thymine in normal DNA and which causes mutations.

Switching to bacteria and the heavy nitrogen system solved many technical problems. By mid-October 1957, Meselson and Stahl had all the experimental pieces in place. Then Stahl went out of town and Meselson performed a dry run. Out came the three bands, just as predicted. The classic experiment worked the first time it was performed. In a narrative characterized by Zen pacing, Holmes signals this climax by stopping the action altogether. Crystallographers sometimes substitute a heavy atom in their molecule, creating a distortion that, viewed from different angles, permits the resolution of ambiguities and the generation of a three-dimensional image. Holmes does this verbally, substituting a memory of Meselson's from 1987 that is inconsistent with the documentary evidence. Meselson remembered running back to the house, bursting in to a noisy crowd, and shouting his success—just like Watson and Crick at the Eagle pub. Holmes tells the discovery story with the recollection and without it, and then he reconciles memory and evidence in a plausible though extremely sympathetic interpretation. This striking chapter offers a glimpse at the strings and pulleys of the historian as he reenacts his play.

Beautiful is not synonymous with interesting. As Meselson himself recognized, the method of density-gradient centrifugation generated more experiments than did the proof of semi-conservative replication. The result was accepted so rapidly that before it was published it was included in a textbook. The Meselson-Stahl experiment, then, is a paradigm case in Thomas Kuhn's original sense. Its significance lies in its confirmation of theory, and in the ingenuity and labor with which its namesakes solved a puzzle of universally recognized importance.

The historian and philosopher of science Stephen Brush once wrote an article (*4*) titled "Should the History of Science be Rated X?" He meant that studies of broad social context and the political motivations of science, questions that interest many historians, may be subversive of scientists' goals. Within science, history provides the origin stories

The author is at the Center for History of Recent Science, Department of History, The George Washington University, Washington, DC 20052, USA. E-mail: comfort@gwu.edu

that root researchers in their fields by conveying the intellectual and technical milestones of the field and attributing credit to its pioneers. For many historians, such stories have the quality of myth. Holmes shows that these stories can be largely true and thus provides a valuable case study for racier scholars. *Meselson, Stahl, and the Replication of DNA* should be rated G, recommended for general scientific audiences.

**References**


1. J. D. Watson, F. H. C. Crick, *Nature* **171**, 737 (1953).
2. H. F. Judson, in *The Eighth Day of Creation* (Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, expanded ed., 1996), p. 423.
3. G. L. Geison, *The Private Science of Louis Pasteur* (Princeton Univ. Press, Princeton, NJ, 1995).
4. S. Brush, *Science* **183**, 1164 (1974).


**BOOKS: ECOLOGY**

# Splendor of Humble Symbionts

**Paula T. DePriest**

Lichens are classic symbioses in the sense of Heinrich Anton de Bary's 1879 "*zusammenleben ungleichnamiger Organismen*." In fact, the term symbiosis had been coined two years earlier by the German lichenologist Albert Bernhard Frank. Lichen-forming fungi, some 14,000 species from a wide variety of groups, live in intimate contact with one or more small photosynthetic partners that are either green algae or blue-green cyanobacteria. Through this symbiosis, the modest filamentous and unicellular partners burst into intricate forms (fruticose beards and treelets, foliose leaves and disks, crustose warts and blankets) and bright colors (chartreuse, orange, red, green). Together, fungus and photosynthesizer form a physiological unit that is amazingly tolerant of even extreme environments, but usually equally intolerant of pollution. If not for their diminutive statue (most are less than a few centimeters tall), lichens might be the orchids of the fungal world. But they are often overlooked and seldom granted such acclaim. Perhaps worse, novices who squint at lichens often mistake them for mosses.


**Lichens of North America**
*by Irwin M. Brodo, Sylvia Duran Sharnoff, and Stephen Sharnoff*
Yale University Press, New Haven, CT, 2001. 819 pp. $69.95, £50. ISBN 0-300-08249-5.

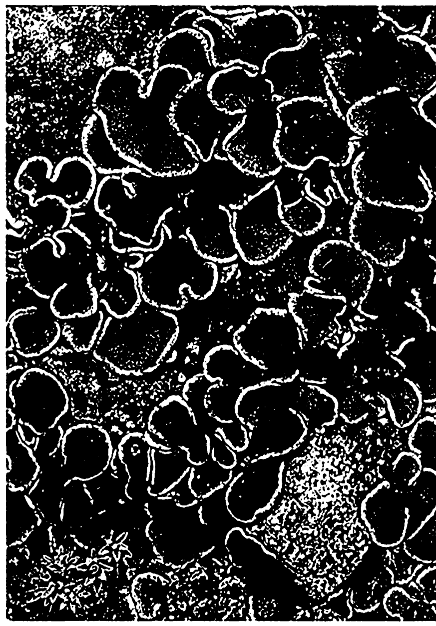

Now lichenology has a photo-illustrated guide that should not be overlooked—the long-awaited *Lichens of North America*. This lavish volume, published in collaboration with the Canadian Museum of Nature, is more than could have been expected: larger, with its 800-plus pages weighing nearly eight pounds; more beautiful, with 939 high-quality color photographs; more complete, with 1500 species covered in detail or mentioned; and more useful, with a 27-page identification key to genera and major groups and separate keys to 1050 species within their respective genera.

The book begins with an overview of lichens, their biology, and their significance. These 113 pages cover topics ranging from "What Lichen Are" to "Collecting and Studying Lichens." Irwin Brodo, an emeritus research scientist at the Canadian Museum of Nature, has produced an accessible and authoritative text appropriate for advanced high school and college biology students as well as professional biologists. Chapters on the impact of lichens, "Lichens and Ecosystems" and "Lichens and People," reflect the special interest of Stephen and Sylvia Sharnoff. To produce an appropriately timeless volume, the discussions of active research areas and internal disputes in lichenology have been simplified and stripped of bibliographic citations. Nonetheless, Brodo is especially adept at shaping the ongoing debates. For example, his brief consideration of the far-from-simple nature of the lichen symbiosis highlights the difficulties in determining whether the partners are "harmonious and mutually beneficial" or the fungi are parasites "exploiting their algal or cyanobacterial hosts."

If the introductory chapters are primarily written for newcomers, amateur and professional lichenologists alike are fully rewarded in the "Guide to the Lichens," which occupies the bulk of the volume. From the estimated 3600 species of lichens in North America, the authors present individual entries for 804 of the most common, conspicuous, or ecologically significant. The attention paid to crustose lichens is a great advance beyond the coverage in previous popular guidebooks. The species accounts include descriptions, photographs, and distribution maps along with brief comments on habitat, variation, and ecological importance. The keys and descriptions are convenient and practical, and the photographs show the species to their best advantage under natural conditions. Most lichens lack "common" names, so the authors present newly coined vernacular names for most of the macrolichens and most genera of crustose lichen. But I am not convinced that such nicknames will make remembering species any easier.

After presenting the species accounts, the authors provide a classification scheme, a glossary, a bibliography, and a taxonomic index. The classification is a necessary but disappointing compromise between developing research and previous systems. In it, and throughout the text, species names are presented without their nomenclatural authorities. Although this information is available through links from a Web site created by the Sharnoffs (www.lichen.com), its inclusion would have provided a stand-alone resource for professionals.

Besides providing such extensive coverage of its subject, *Lichens of North America* is a masterpiece of photographic illustration. The page design and layout add to the volume's beauty. Photographs appear to float within the generous margins. The colors are subtle and completely natural. Whether illustrating orange and yellow lichens draping over rocks, gray lichens veiling a serene gravestone angel, or yellow-green grandfather's beard festooning trees in a Cascades forest, the images are technically superb and printed with excellent resolution, sometimes at nearly five times life-size. They present what previously could only be seen through a hand lenses. But more important, they show lichens—even the hard-to-portray greenish-black *Collema* and *Leptogium*—in perfect field conditions. Readers interested in learning how these images were captured will enjoy the introductory section "Photographing Lichens: Techniques and Advice."



**A colorful scale.** *Psora pseudorussellii* is found on limestone exposures from southern New England across the Midwest to Texas.



The book is the result of a symbiosis among the authors themselves. Irwin Brodo produced excellent text that is factual and interesting. Sylvia and Stephen Sharnoff took the high-quality photographs over more than a decade of relentless travel throughout North America. Unfortunately, Sylvia Sharnoff,

The author is in the Department of Systematic Biology–Botany, W-525, National Museum of Natural History, Smithsonian Institution, Washington, DC 20560, USA. E-mail: depreist.paula@nmnh.si.edu