BOOK REVIEWS

The Entrepreneurial Twist

The Billion-Dollar Molecule. One Company's Quest for the Perfect Drug. BARRY WERTH. Simon and Schuster, New York, 1994. 445 pp. $25.

Many scientists trace their interest in a scientific career to a reading of Paul de Kruif's *Microbe Hunters*, published in 1926. In that work de Kruif described the adventure of scientific discovery in the study of infectious disease starting with Leeuwenhoek and extending through Walter Reed in the early 20th century. De Kruif drew his subjects as lone scientific pioneers and romantic societal heroes. A half-century after *Microbe Hunters*, the Alfred P. Sloan Foundation commissioned the autobiographies of a number of great scientists of the mid-20th century in an effort to promote public interest in science. The Sloan books portray their adventurers most often in the setting of academic or public research institutes, and, unlike some of de Kruif's lone heroes, the Sloan subjects have been revered in their own time. A flurry of recent books now continues to portray the scientist as adventurer and social hero. A contemporary twist is that the scientist has also become an entrepreneur.

Emblematic of the scientist/hero/entrepreneur's story is Barry Werth's *The Billion-Dollar Molecule: One Company's Quest for the Perfect Drug*. The "perfect drug" is an immunosuppressant to be used in the organ transplant setting, and the site of the quest is a start-up biotechnology company, Vertex Pharmaceuticals. Werth's hero is Josh Boger, a brash scientist who at the start of the book has recently left Merck to found Vertex. Boger promises to build a next-generation pharmaceutical company using a 1990s paradigm for drug discovery. He argues that he will do at Vertex what he couldn't do at Merck. In the manner of many new entrepreneurs, he promises that the proof of his model will be a drug that has eluded many. At the close of the narrative the company has been well established, although the drug has still not been attained.

This is a fascinating and complicated story woven together of several strands. One strand is the evolving paradigm of drug development. In the early 1900s, drug discovery was serendipitous. Werth shows how the brute-force screening of plant extracts and chemicals employed at Merck and other companies eventually gave way to more "rational" drug screening programs in which the target against which screening is performed is a purified molecule (such as a receptor or an enzyme responsible for a known phenomenon. This so-called "rational drug screening" paradigm has further evolved in the past decade into "rational drug design." Here computer-aided molecular modeling is employed to design small molecules that can be synthesized and then empirically tested for activity against the purified biological target. This latest approach is the one championed by Vertex.

Another strand of the story is the shift of fundamental research from the public to the private sector. Werth has written a well-researched (but overly lengthy) narrative that follows Boger's fortunes. As the book opens, Boger is raising money on Wall Street. The narrative traces Vertex's attempt to implement its drug-discovery approach in parallel with the building of the company. This story is juxtaposed with that of another scientific pioneer in organ transplantation, the Pittsburgh-based transplant surgeon Tom Starzl, and his efforts to use another promising immunosuppressant, FK-506. There are fascinating parallels between Boger and Starzl despite the differences in their generations, between their specialties (surgery and drug design), and between the academy and Wall Street. For this reader, this comparison is the most interesting and revealing part-of Werth's book. Both protagonists are single-minded in their determination to be first in achieving the perfect immunosuppressant. One can easily draw the conclusion that the exact same sets of skills are needed by the two men despite the differences of the public and private venues. Both men's efforts are set against professional and personal rivalries played out in international scientific forums. In Boger's case the result of the battle can be traced on a daily basis in the close of his company's stock price.

A third strand in Werth's narrative relates to the issues of building a technology-based company. Here *The Billion-Dollar Molecule* joins Stephen Hall's *Invisible Bullet*, Robert Teitelman's *Gene Dreams*, and Natalie Angier's *Natural Obsessions*. Each of these works—to a different extent—is a biotech version of Tracy Kidder's *Soul of a New Machine*, the now-classic book (and the very best of the genre) that chronicles the early days of the computer industry. Taken as a class, these books show that the attributes ascribed by Werth to Boger and Vertex are really common characteristics of the scientist/entrepreneur. In fact, the self-confidence and seemingly inexhaustible energy that fuel Boger are the same that fueled the scientist-heroes of *Microbe Hunters* and the Sloan series.

The founders of the more than 1000 start-up biotech companies are driven people who each believe they are truly special and are determined to succeed. Clearly, all can't. Biomedical research is a capital-intensive enterprise, and not all young companies will have sufficient capital to bring their efforts to closure. Thus Werth's book, read as a metaphor for the biotechnology industry, has clear lessons for both the investment community and those concerned with the future of biomedical research. Research is a high-risk, high-reward venture regardless of whether it is done in public- or private-sector settings. When the fortunes of a company's stock rest on the progress of its fundamental research the buyer had best beware. And those who are confident that basic research will be richly supported by the public markets should ask whether the markets will continue to support young biotech companies when research falters and stock prices decline.

Those who read *The Billion-Dollar Molecule* will also learn how seductive but difficult simultaneous success in research and business can be. And among young readers, I suspect that the story will nurture many an entrepreneurial-scientist dream.

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Genomic Odyssey

Travelling Around the Human Genome. An *in situ* Investigation. BERTRAND JORDAN. INSERM, Paris, and Libbey Eurotext, Montrouge, France, 1993. x, 188 pp., illus., + plates. Paper, $35 or F 180 or £22.

Voyage Autour du Génome. Le Tour du Monde en 80 Labos. BERTRAND JORDAN. INSERM, Paris, and Libbey Eurotext, Montrouge, France, 1993. x, 182 pp., illus., + plates. Paper, $35 or F 180 or £22.

Travelling Around the Human Genome: An in situ Investigation provides an excellent overview of the international collaboration

and competition that have arisen in response to the challenge of unraveling the human genetic database. It grew out of a series of articles published at regular intervals starting in 1990 in the French periodical *médicine/sciences*. The reworking in book form, which, in the English translation at least, retains some of the flavor of the original articles, has been aimed broadly at "a relatively wide community of biologists, medical doctors and others interested in the topic."

Jordan writes persuasively; indeed, his talents in this area can be gauged from the support he was able to raise for his sabbatical plan to travel around the world and visit a selection of human genome research centers. In the first part of the book, an outline of the agenda of the human genome program is followed by a description of how genetic and physical maps can be produced. There is a certain lack of consistency in this account, and occasionally the chasm between the lay reader and the cognoscenti (of which Jordan is one) is exposed. For example, the nature and significance of yeast artificial chromosomes (YACs) are described in considerable detail, but then the term "cosmid" (a type of small-scale bacterial equivalent) is used with hardly any explanation. Nevertheless, the attempt at enlightenment is worthwhile and well illustrated.

Jordan goes on to highlight the apparent conflict between the objectives of reverse genetics (that is, positional cloning, dedicated to the isolation of individual genes from defined chromosomal regions) and the goals of the genome program (which demand mapping and sequencing on a much broader front). Although it is true that several laboratories may enter into apparently wasteful competition in order to isolate a key gene, the stimulus provided by such a prize can be instrumental in generating innovation and new technology. The importance of the funds provided by various charities, which have had an enormous impact in determining the direction of research, is not emphasized sufficiently. In addition to providing a specific focus, such organizations can play a significant role in reducing unnecessary overlap, as illustrated by the Muscular Dystrophy Association of America's orchestration of the research of several teams striving toward the isolation of the myotonic dystrophy locus. Strangely, considering that the isolation of a candidate gene for this extremely prevalent disorder represents one of the major successes of positional cloning, it is mentioned only once, and even then only in passing. Jordan complains that the targeted gene approach is "a situation reminiscent of cartographers responsible for preparing an overall map of a country who would survey solely those sites liable to contain oil deposits." The point is well taken—but, to continue the analogy, surely if one is exploiting new territory it makes more sense to bore oil wells than to sift sand.

Subsequent sections of the book provide a useful discussion of genome sequencing technology and its pitfalls and a pragmatic evaluation of the likely amount of time needed to complete the task. In discussing "high-tech" approaches, Jordan hits on the key fact that both mapping and DNA sequencing in isolation are tedious occupations and, once under way, provide little opportunity for those involved to develop scientific, as distinct from technical, skills. Motivation is an essential ingredient that may be in short supply in some genome endeavors. Overall, credit is given where deserved and the independent yet complementary roles played by microsatellites, YAC gridded libraries, complementary DNA (cDNA) isolation, and dedicated sequencing are given balanced treatment.

"HUGO in high seas." *Left to right*: Bertrand Jordan; Charles Cantor, active on behalf of HUGO in the United States; Elizabeth Evans, of HUGO's European office in London. [From *Travelling Around the Human Genome*; picture taken during the 2nd European HUGO meeting in Sardinia, April 1992]

Rather surprisingly, the sections that I thought would be least satisfying turned out to be full of insight, providing an amusing and reasonably convincing analysis of the impact of culture and social structure on the strategies adopted by the various national projects. Perhaps not enough credit is given to the contributions of the Human Gene Mapping Workshops, which have provided continuity in the field since 1973 and, together with the Baltimore-based Genome Data Base, have been responsible for the publication of edited cytogenetic location tables and genetic and physical maps—an essential service for the mapping community. More recently, these have been supplemented by single-chromosome workshops organized in conjunction with the Human Genome Organization (HUGO), which have provided both a stimulus and a focus for more widely based genome interests. Given the sometimes competing aims of national programs and the conflicting objectives of funding agencies, the hope must be that HUGO's status as a truly international coordinating body will be generally recognized.

The book's style is of the condescending "science can be interesting if presented properly" genre. There are subheadings on every page, ranging from such important insights as "Craig Ventner's interests extend beyond cDNA" to such illuminating comments as "Data processing is taken seriously." It has also proved difficult to hide the fact that the book is based on a collection of articles, and often the same points are made several times. In spite of this redundancy—indeed, even because of the fact that it is frequently superficial and idiosyncratic—it is quite fun to read.

Maybe the "take-home" message from Jordan's "travels" should be that good organization, relatively small teams, and motivation are just as important to the success of a large project as mega-funding—a point well illustrated by the publication in December 1993 of the Centre d'Étude du Polymorphisme Humain (CEPH)–Généthon first-generation physical map of the entire human genome.

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The Structure of Memory

Memory, Amnesia, and the Hippocampal System. NEAL J. COHEN and HOWARD EICHENBAUM. MIT Press, Cambridge, MA, 1993. xiv, 330 pp., illus. $45 or £40.50.

The hippocampal formation has intrigued neuropsychologists and other neuroscientists since the report in 1957 of patient H.M., who underwent bilateral removal of this structure, together with surrounding brain tissue in the temporal lobes. This somewhat desperate surgery was performed to prevent life-threatening epileptic sei-