Triumph of the heart

The story of statins

Jie Jack Li
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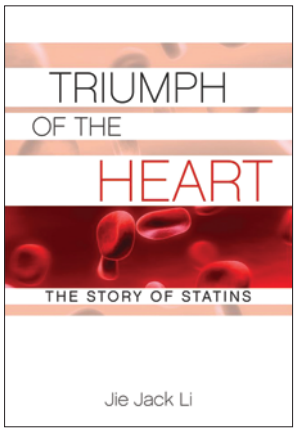

Triumph of the heart: the story of statins by Jie Jack Li actually comprises several books in one — threads that run through the chapters as concurrent streams. The most compelling story recounts the checkered history of the development of the cholesterol-lowering drugs of the hydroxymethylglutaryl coenzyme A (HMGCoA) inhibitor family, also known as statins. This narrative illustrates the principle that most "breakthrough" drug development programs succeed despite, rather than because of, upper management and often depend on the ardent advocacy of individual scientists. The book describes the struggles of key protagonists in the development of statins. A few individuals emerge as heroes who pitted their passion and persistence against countervailing forces in their own industry.

In one poignant passage, Akira Endo, the discoverer of statins, packs his office belongings and carries them out of his laboratories at the former Sankyo Corporation unaided; his colleagues had received instructions not to assist him after upper management discharged him. Such was Endo's reward for having shown the creativity of targeting HMGCoA reductase, and for his persistence and dedication in developing the first statin.

Likewise, the tableau of Roger Newton falling to his knees to plead for bringing atorvastatin into clinical evaluation at a 1990 meeting with senior executives at Parke-Davis appears more like a scene from a swashbuckler novel than from a corporate meeting room. Newton's persistence and courage single-handedly saved the atorvastatin program from the drug development dustbin. The portrayal of the travails of the Parke-Davis medicinal chemistry team, directed by Bruce Roth, in developing atorvastatin gives the reader a glimpse into the hazardous undertaking of the design of new molecules suitable for use as drugs.

A third hero of the statin development drama, Alfred Alberts of Merck, encountered fewer problems in developing lovastatin. But a decision by upper management put the clinical evaluation program on hold for several years, delaying the availability of the first statin on the market in the United States. If Alberts and his team had not had the good fortune of finding a "hit" in the 16th sample that they screened for HMGCoA reductase inhibition, they too might have encountered the kind of obstacles from management that plagued Endo and Newton.

These three tales illustrate amply the human factor in drug development in Big Pharma, the role of chance, and the dependence of almost every successful drug development program on a "champion" who often persists despite internal opposition. Therein lies the value of Li's story of statins.

The other streams running through the book either seem tangential or have been better told before. Daniel Steinberg's authoritative "interpretive history" of the "cholesterol hypothesis" of atherosclerosis, its challenges and ultimate vindication, remains unmatched (1). The sketches in Li's book of the histories of various pharmaceutical firms are interesting, but forays into the development of antibiotics, steroid hormones, and epinephrine distract from the thrust of this tale, having little to do with statins or the heart. Venerable accounts describe better Paul Ehrlich's development of the antisyphilitic agent Salvarsan and Alexander Fleming and Howard Florey's work on penicillin, among other examples unrelated to cardiovascular pharmacology dwelt upon in Li's book (2).

Li's background as a medicinal chemist shines through in his detailed depiction of the academic genealogy of key contributors to the chemistry discussed in this book. He relishes the details of the chemical challenges, including the complexities of chiral syntheses. These long digressions will not interest general medical or lay audiences, but they will engage more chemically minded readers. The "chemical" passages compel most when they furnish unvarnished views into scientists' human foibles and how they influence the research enterprise.

Given Li's background and interest in drugs that target lipid metabolism, some of the book's factual lapses seem surprising. The discussion of fibrate-statin interactions does not mention the defect in glucuronidation of some statins, particularly due to gemfibrozil. One allusion to the ENHANCE trial (which assessed the effect of ezetimibe plus simvastatin versus simvastatin alone on carotid intima-media thickness) misrepresents the end point as "reducing coronary heart disease." The editorial comments characterizing as sad or regrettable the FDA halt on laropiprant (a prostaglandin D receptor antagonist intended to decrease niacin's side effects) detract from the book's balance. Finally, the use of brand names rather than generic designations lends a commercial patina to the text, although an appendix of the names does provide a concordance.

Despite these drawbacks, *Triumph of the heart* provides documentation of some of the "oral history" of the story behind the story of statin development. The depiction of the champions of this important undertaking affirms their critical contributions to lowering cardiovascular morbidity and mortality worldwide. Their uphill battles bear notice by pharmaceutical executives as they struggle to find the path for the future of their industry.

1. Steinberg D. *The Cholesterol Wars: The Skeptics vs. the Preponderance of Evidence*. San Diego, CA: Academic Press; 2007.
2. Silverman M. *Magic in a Bottle*. New York, NY: The Macmillan Company; 1948.