

Merck work



Hallelujah Moments: Tales of Drug Discovery

BY EUGENE H. CORDES

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Staring at the front cover of *Hallelujah Moments*, I'm drawn to the circular halo filled with soft, fuzzy just out-of-reach golden shapes. Am I gazing into heaven? Or, more intriguingly, looking into a round-bottom flask filled with the next prospective Merck wonder-drug?

This semi-autobiographical science tale comes courtesy of Eugene Cordes, formerly a Merck vice-president and now a professor at the University of Michigan at Ann Arbor. Readers may recognize his name from *The Tao of Chemistry and Life* (reviewed here in 2009); his latest effort announces an almost ideological successor.

Merck has developed many of the world's top drugs, several of which were the subject of Dr Cordes's attention in his twenty years with the company. A natural 'Greatest Hits' collection follows. Finasteride, an early steroid antagonist, helps alleviate prostate enlargement. Early angiotensin-converting enzyme (ACE) inhibitors, distant relatives of snake venom, lower blood pressure. Sitagliptin triumphs as a structure-based, selective dipeptidyl peptidase 4 (DPP-4) inhibitor to treat type 2 diabetes. Readers also get a dose of risky antibacterial research and a real grasp of the challenges of the isolation of natural products. It's not all about success: the fludalanine flop illustrates that a solid hypothesis (bacterial enzyme inhibition), good safety window, and even some mechanism-based drug design (one of the first examples of deuterium-labelled 'heavy' drugs) still doesn't produce a new antibiotic. The author pithily sums this up: "Nice try, no Hallelujah."

Much like *The Tao of Chemistry and Life*, Cordes starts at the very beginning, using his first few chapters to introduce the concept of atoms and molecular bonding. He then expands outwards to basic biochemistry and proteins before diving into

full-scale drug campaigns. As we advance along Cordes's career track, we're treated to a wider perspective: more tough management decisions and ancillary drug studies.

Unfortunately, while discussing human clinical trials (Chapter 12) the approachable style falls away in favour of data overkill — the section reads like a *New England Journal of Medicine* abstract.

I greatly appreciated some of the trivia thrown into the mix — these tongue-in-cheek moments help break up some of the denser material. For me, the most memorable examples are the nickname 'gorillamycin' given to Primaxin — a novel antibacterial — earned for its sheer power against numerous infections, and that the cholesterol-lowering statins were a chance discovery by a hyper-productive Japanese scientist on sabbatical. Cordes also notes that in the early days of antibiotics, it was common to re-extract penicillin from patients' urine and that the avermectins were isolated from a bacterial culture found outside a golf course (perhaps a justification for the seemingly endless popularity of golf with executives?). Finally, on the more bureaucratic side of the pharmaceuticals business, he notes that FDA paperwork was once enough to quite literally "fill a truck".

Many of the author's metaphors help to explain otherwise tricky concepts. I enjoyed the analogy of the human circulatory system to a giant water balloon (Chapter 6), and his rather illustrative examples of how negative feedback operates in the body. The analogies offered for the drug-discovery process, however — climbing Mount Everest, an adventure movie, a complex maze with many entrances — felt trite and stale.

Although the author eagerly anticipates that his 'little book' will help to 'fight scientific illiteracy', this reviewer doesn't predict a groundswell. The stories suffer from a strangely pedantic tone — Cordes has authored several textbooks, and the chapter structure of *Hallelujah Moments* bears that hallmark. The conversational tone applauded by dust-jacket reviewers quickly deteriorates into jargon. Frequent hat-in-hand apologies to lay readers ("I understand that's a difficult and meaningless word to many...") feel mildly condescending. Random learned Latin phrases (*sequelae*?) and thesaurus-worthy words don't exactly inspire inclusive feelings.

Full chapters could have benefited from serious sculpting by a heavy editorial hand. Verb tenses are muddled and sentences start to repeat themselves ("Here is why..."). Many of *Hallelujah's* schemes feel like afterthoughts; I found the tiny font and figure legends particularly vexing. Perhaps Carl Zimmer's writing advice to "kill your darlings" applies — the author seems very fond of lists. Genera of Gram-positive and -negative bacteria; drug classes; parasite types; cephem antibiotics; Nobel laureates. My meta-list barely does these justice.

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Certain stylistic choices slow the overall momentum. I missed the messy yet personal vignettes of books like *The Billion Dollar Molecule* or *The Double Helix*. In the Merck autobiography arena, Roy Vagelos's retrospective *Molecules, Medicines, and Merck* invokes more personal struggle and emotion than *Hallelujah* in its best moments. We also suffer a fair dose of hero worship: any Nobel Prize winners even tangentially related to the story are mentioned. And although Merck scientists are called out by name, checking off their specific contributions to each project, the recognition feels somehow cold and perfunctory. Precious little comparison between Merck and other companies — except for the discussion of statins and diabetes drugs — makes it seem sometimes as though Merck were the only company discovering useful drugs!

Nevertheless, Cordes's book does eventually deliver interesting drug-hunting tales from a Merck discovery insider. I wouldn't necessarily recommend it for the armchair chemists in the audience. Who might best appreciate *Hallelujah Moments*? Life-long Merck employees, or perhaps young medicinal chemists that need a sense of Merck's history and place. □

REVIEWED BY MICHAEL A. TARSELLI

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