TALES OF DRUG DISCOVERY

HALLELUJAH MOMENTS

Eugene H. Cordes

Hallelujah Moments

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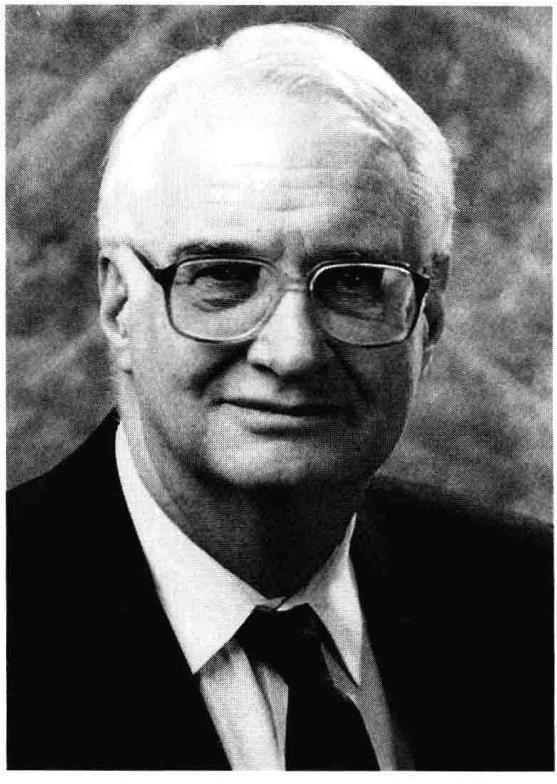
Dedicated to the memory of Ralph Franz Hirschmann



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Preface

TWO THINGS ARE absolutely clear. First, science and its synergistic partner technology are really important in our daily lives, now and going forward. Second, the general population, both in the United States and abroad, suffers from a high degree of scientific illiteracy. As a general rule, we are ignorant of what is really important to all of us.

It is much easier to list things for which science and technology matter critically than to list things for which they do not. Science and technology are at the heart of human and animal health, agricultural productivity, climate change, communications, national defense, economic progress, personal wealth, travel, space exploration, environmental protection, biodiversity, understanding of human history, protection from the elements, and on and on. I will leave it to you to list matters that affect human well-being that are somehow independent of science and technology.

All the matters listed in the previous paragraph are fodder for policymaking. How much of the national treasure should be invested in our science-based federal organizations, including the National Institutes of Health and the National Science Foundation? How do we handle genetically modified foods to ensure both human health and economic growth? What should we be doing to ameliorate global warning and prepare for its consequences? How should we invest to ensure that we have access to clean water and clean air? How do we best protect the abundant biodiversity that our planet offers? What investments in advanced weapons systems will provide maximal national protection at tolerable cost? Should we invest more national treasure in space exploration and, if so, how?

These and related issues are frequently areas of national contention. Given that reasonable and informed people will legitimately disagree on priorities and prospects, it is also true that much of the contention derives from ignorance. Were we, as a people, better informed about science, many of the arguments would fade, better policy decisions would be made, and we would all be better off for it. The people concerned most directly with national policymaking—our senators and representatives—are no better informed on scientific issues than the general public. And our state senators and representatives are no improvement over those at the federal level.

Scientific illiteracy leads to all sorts of problems. Almost any change will lead some people to perceive themselves as losers as a result of the change. They will fight back with whatever means they have at their disposal, fair or foul. To the extent that we are ignorant of the evidence or cannot judge the validity of the evidence relating to the change accurately, we are victims of those who attack falsely to ensure their personal or corporate benefit.

I can think of no better example than that of the tobacco industry, which effectively resisted evidence of the health threat of tobacco use for years after it was clear to all informed people the threat was real and urgent. Cigarette smoking remains the largest single threat to human health. Through misdirection, misrepresentation, bad science, and creation of a sense of uncertainty where none existed, the tobacco industry protected their profits for years at the expense of a profound negative impact on human health. Our ignorance let the tobacco industry get away with it.

Such stories continue. Specious arguments about global warming, for example, are everywhere, promoted by those global-warming-deniers who see themselves as losers should effective action be taken to combat the real threat. Whether bad policy and bad decisions derive from ignorance or venality, they affect society adversely. We need to do better.

My hope is that this little book has some modest impact on scientific literacy. It seems sensible to me to write about something that I understand. I have spent half of my professional life as a professor of chemistry and biochemistry, and the other half as a scientist doing drug discovery and development in the pharmaceutical industry, so that is what I know most about.

Getting new and useful drugs in medical practice is both important to human health and is understood poorly outside of pharmaceutical houses. It is, I believe, worth knowing about. Beyond that, drug discovery is, in a very real sense, an adventure story. Climbing Mt. Everest is an undertaking in which courage and stamina battle extreme cold, excessive winds, and high altitudes. Gripping adventure stories result. So do failures. Drug discovery is an undertaking in which wit and determination battle uncertainties in human physiology, issues of molecular design, and questions of how to interpret data in the face of regulatory uncertainties. Gripping adventure stories result. So do failures. When you start an ascent of Mt. Everest, your chances of getting to the summit are really pretty good. When you start a drug discovery project, your chances of creating a successful

human health product are rather dismal. Ascending Mt. Everest gives you a story to tell. Making a drug has far-reaching consequences, including a positive effect on human health worldwide, which gives you a story to tell.

The early part of this book provides background to help you understand the tales that follow. The tales are adventure stories. I hope you understand them, learn from them, and are amused by them.

One theme that affects most of these stories is the role of basic research in providing the inspiration or knowledge base for success in drug discovery and development. For example, basic studies in human genetics and hormone physiology laid the foundation for the discovery of finasteride (chapter 6); the discovery of angiotensin-converting enzyme (ACE) inhibitors (chapter 7) relied on an understanding of blood pressure control, the chemistry of snake venom peptides, and a novel enzyme inhibitor design; discovery of the statins (chapter 8) followed an understanding of the role of cholesterol in human physiology, the biosynthetic pathway to cholesterol, and elucidation of the role of the low-density lipoprotein receptor in control of cholesterol metabolism; and the discovery of sitagliptin and its relatives (chapter 12) depended on knowledge uncovered by the Human Genome Project.

This basic scientific information was developed, in great measure, in academic laboratories and then exploited by the pharmaceutical industry to the benefit of people worldwide. Although basic research may seem arcane or even pointless, the fact is that it is the best investment in wealth creation and human welfare that can be imagined.

A good bit of the ground covered in the drug discovery and development chapters has been revealed in a different context in the book *Basic Research, Medicine, and Merck* by Roy Vagelos and Louis Galambos. You might wish to have a look at that book as well.

Acknowledgments

MANY PEOPLE HELPED me get these stories straight. Without their thoughtful assistance there would have been little here worth reading. I owe thanks to

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My sincere thanks go to all the individuals mentioned here. Whatever in this book remains unclear, incomplete, or simply wrong is my sole responsibility.

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