What I have learned from Jim.

You have been called honest Jim; moral, indignant Jim; impatient, excited Jim; visionary, romantic Jim – and even outrageous, outspoken, Jim. For someone seemingly born with the genes for a reticent disposition, you have come an amazingly long way in your 70 plus years.

A keen observer of human behavior, with a sharp focus on the many fallibilities and incongruities that produce a large reservoir of gossip, you are deeply interested in people. Perhaps that is why you noticed me as a 22 year-old first-year graduate student at Harvard who had attempted, with the overconfidence of youth, to explain the molecular basis for much of genetics. My predictions of mechanisms ranged from the initiation of DNA replication to homologous genetic recombination – all in a paper of about 25 pages.

I had based my speculations on what I had learned as a Harvard undergraduate in Paul Doty's laboratory about DNA renaturation (now known as DNA hybridization) and the structure of single-stranded nucleic acids. [1] Like all of my contemporaries, I had been inspired by your 1953 discovery (with Francis Crick) of the DNA double helix – a discovery then only eight years old.[2] But I had falsely concluded from that remarkable breakthrough in our understanding of living organisms that biological systems would turn out to be not only elegant, but also relatively simple. As a corollary, both my fellow graduate students and I believed that – with some careful thinking guided by a few elegant experiments – scientists should be able to predict all of the basic genetic mechanisms from a few fundamental principles. At any rate, this was the underlying assumption of my term paper.

It is now forty years later, and biological systems have turned out to be enormously more complex than any of us ever anticipated. Most cellular reactions are controlled by large multi-protein machines whose behaviors can only be dissected through a decade or more of careful *in vitro* experiments.[3] These machines have evolved over billions of years through long pathways of mutation followed by natural selection, and their final structure is partly an accident of history. Thus, although each is a very cleverly engineered device, few have turned out to be even roughly

predictable – to the great frustration of two generations of theoretical biologists. Thus, what I first learned from you was both inspiring and somewhat misleading. But your interest and encouragement made such a great impression on me as a graduate student that I still remember the details of our conversation.

I was flattered by your reaction to my paper. Your enthusiasm for the then-novel idea that DNA polymerase starts at the 3' end of a single-stranded DNA template, using a hairpin helix as the primer, led to my attending your group meetings as an outsider from the Doty lab. There I became fascinated with the thesis project of your student John Richardson, who was studying the DNA binding properties of *E. coli* RNA polymerase. John had shown that, even though this enzyme binds to specific DNA sequences inside the cell, it also binds much more weakly to any DNA sequence. Later, this finding would provide the inspiration for the project that I designed for my postdoctoral year in Geneva, Switzerland – aimed at developing DNA-affinity chromatography.

But my pursuit of DNA-affinity chromatography would only come after I had become thoroughly disillusioned with repeated attempts to predict biological mechanisms from first principles. The attempt to confirm some of the predictions in my paper with highly focused experiments formed the basis for my research for a Ph.D. degree. Not surprisingly, these were frustrating years. To guess at a mechanism and then perform an experiment that only makes sense if that mechanism is correct is a low-yield, high-risk strategy for any biologist.

Quite unexpectedly, I failed my initial thesis exam in 1965. This shock, coming after 4 years of research, forced a complete rethinking of my approach to science. My post-doctoral year in Geneva was delayed by six months by the need to retake my exam. This gave me plenty of time to plan a very different approach to biology. In the end, I decided to try to develop a method that should provide important new information independent of any theory: I would attempt to make a chromatography column out of DNA. . This DNA affinity column would hopefully attract all of the many proteins in a crude cell extract that normally bind to chromosomes, allowing me to purify these proteins away from the vast excess of other proteins that function elsewhere in the cell. Studies of subsets of these purified proteins might then lead to a detailed understanding of genetic mechanisms, independent of any speculative theories.

Fortunately for me, you spent your sabbatical in Geneva with Alfred Tissieres, who was also my official post-doctoral advisor. Despite your 1962 Nobel Prize, you were very accessible, frequently strolling from room to room to listen to the latest results from each post-doc in Tissiere's large laboratory and provide advice. You seemed to believe that my approach was too much like "Swedish science," meaning that it focused on developing a method, instead of being a direct attack on an important biological mechanism.

Because my previous 5 years at Harvard had been all imagined biology with very little in the way of results, I persisted nevertheless. By the end of my year in Geneva, a promising technique called DNA cellulose chromatography was born. In 1969, this method would allow my new laboratory at Princeton to discover and characterize the first "single-strand DNA binding protein," – a central part of the multi-protein, DNA replication machine.[4]

In early 1966, on a train from Geneva to St. Moritz for the traditional lab ski week, we all finally discovered what had helped to motivate your sabbatical. Typed copies of individual chapters designed for a new book magically appeared, passing from seat to seat and from car to car. These were draft chapters from The Double Helix. Beautifully written, we were amazed by each chapter and couldn't stop reading. I especially remember my delight in encountering your humorous description of the young Josh Lederberg at the start of what would become Chapter 20: a brilliant scientist with the "godlike quality of each year expanding in size," perhaps eventually to "fill the universe".[5]

You were unmarried in 1966 and interested in beautiful, intelligent younger women. My wife Betty and I were quite amused to be recruited as escorts in St. Moritz to aid in your search for romance. Betty will always remember how kind you were to her when she broke her leg at the end of that ski week. And by the time that my post-doctoral year was over, I felt that the three of us had become friends.

The Double Helix served as a centerpiece for the first course that I taught as a beginning Assistant Professor at Princeton in 1968. By then, your recently published book had not only been universally acknowledged as great scientific history; it had also triggered a widespread debate about the

motivation of scientists. Were we mostly motivated by a search for fame and Nobel Prizes, as some had read into your autobiography? If so, were our motivations no more admirable than those of our contemporaries seeking fortunes in the world of business? The possibility was disturbing to me and to many Princeton graduate students. For years, my annual required graduate school course on "the physical chemistry of macromolecules" therefore began by having the students read and discuss "Priorities in Scientific Discovery" by R. K. Merton[6] and "Motivation Reconsidered: the Concept of Competence" by R.W. White[7] – along with The Double Helix.

From many deliberations of this kind, I have concluded that most scientists are driven by the challenge of solving important problems – and by the deep pleasure derived from the feeling of competence that comes from surmounting them (White's "competence principle" – as also experimentally demonstrated with chimpanzees). This view was derived directly from the challenge of your book, and it has provided me with a critical lens for viewing both science and the broader world of humanity.

In the early 1970's, I was appointed to be the Princeton representative on the Cold Spring Harbor Board of Trustees. I was therefore in a good position to follow the amazing transformation that you produced at the Cold Spring Harbor Laboratory as its Director, the position you assumed in 1968. Never satisfied with what you had already accomplished, you continually pushed for new buildings and new scientific programs. Once, when the Board turned down a particularly expensive request, you gave us 10 minutes to change our mind. Then you left the room, saying you would otherwise resign. The Board – headed by a distinguished New York banker -- of course acquiesced, and the Laboratory continued to prosper with you as its visionary leader.

The same type of stubborn, forward-looking vision – clearly exhibited by your own science and by all that you have accomplished at Cold Spring Harbor – also proved to be critical for establishment of a successful Human Genome Program at the National Institutes of Health. As a key member of the study committee that I chaired at the National Academy of Sciences in 1987-88, and later as the Program's first director, you saw clearly what most of the scientific community could not see – that such a special program, if properly defined and structured, would greatly accelerate progress in all of biology.[8]

My many interactions with you have taught me something very important about leadership. Successful new initiatives generally originate from the inspiration and energy of one or a few individuals, not from a general consensus. One can expect that, at the start, any bold new idea will seem unreasonable to most people. Therefore, an unreasonable persistence will often be required to move society forward.

After time passes, and a bold new idea has proven to be successful, most people will insist that the once-ostracized idea had been obvious all along. In this way, we trivialize the entire history of human achievement. And we mislead the next generation of young people into thinking that the only ideas worth pursuing are those that make sense to the majority. Hopefully, the terrific success of the Cold Spring Harbor DNA Learning Center, which you started as a bold new idea in 1987 – plus the many related educational efforts that it has since spawned for high school students around the nation – will help to dispel this debilitating myth for the next generation.

I cannot end this brief essay without emphasizing the tremendous part that you have played in producing a new generation of textbooks in cell and molecular biology. The *Molecular Biology of the Gene* appeared in 1961, as I transitioned from an undergraduate to a graduate student at Harvard. For the first time I understood the reasons for many aspects of cell chemistry – for example, the logic of deriving the specificity of molecular interactions from the sum of many weak non-covalent bonds.[9] So when you phoned in early 1978 to invite me to be one of your coauthors on a new type of textbook that you had invented – the *Molecular Biology of the Cell* – I immediately accepted.

Had you provided me and the other four authors (Martin Raff, Keith Roberts, Julian Lewis, and Dennis Bray) with a more realistic estimate of the time that would be required from each of us to write the first edition of this book, it is unlikely that any of us would have agreed to begin. What was advertised as an effort requiring only two summers turned out to involve an exhausting series of book meetings that required more than 365 twelve-hour days from each author. These extended over Christmas, Thanksgiving, and many other missed family occasions. But once again you had it exactly right. The time had indeed come to unify the traditional discipline of cell biology (then based mostly on light and electron microscopy) with the exploding newer discipline of molecular biology (based on biochemistry and genetics). The *Molecular Biology of the Cell*, published in 2002 in its 4th

edition, will have sold more than a million copies before the 5th edition appears.[10]

Because of your two major textbooks, extending over 40 years, an enormous number of scientists have greatly expanded their view of biology. I include here all of the authors, who have learned an enormous amount about both biology and clear writing through the privilege of working with you and each other on these important education projects.

To conclude, Jim, I have learned many important lessons from my close interactions with you over the years. First, to expect elegance and simplicity from biological mechanisms (even if the simplicity part was wrong); second, to view the motivations of my fellow scientists as noble ones, based on a search for understanding and a feeling of competence; third, that leadership works best if it is bold and does not always seek consensus; and – last but not least – how to think about biology much more conceptually and broadly.

For my entire generation of cell and molecular biologists, it has been a great ride, and I thank and congratulate you for the many roles that you have played in making it possible.

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