

FROM YOUTHFUL CURIOSITY TO A CAREER IN SCIENCE

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Introduction:

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As an aspiring biochemist/physician who came of age in the second half of the 20th century, my scientific experience was akin to being present at “the creation.” In 1944, Avery, MacLeod, and McCarty published data demonstrating that genetic information could be transmitted from one cell of a pneumococcus bacterium to another by purified DNA.

Oswald Avery was a physician who got his medical degree at Columbia, and after practicing medicine in New York, became a member of the Rockefeller Institute. The tone of this seminal publication was dry and modest, but Avery *et al* were far ahead of their time and it took nearly a decade for their work to elicit published recognition of the significance of their discovery.

When I took my first biochemistry course at Harvard in 1951, our textbook had almost nothing in it about DNA, let alone about the discovery made by Avery, MacLeod, and McCarty. That paradigm-shifting discovery was never recognized by a Nobel Prize. In scientific circles, however, the work of Avery *et al* had not gone unnoticed. A few years after I took my first biochemistry course, James Watson dropped by George Wald’s lab at Harvard, where I was working at the time and discussed the discovery that he and Francis Crick had made about the structure of DNA. That discovery was also extraordinary, namely that DNA consisted of two complementary strands that were wound around each other in a helical fashion. They proposed that the complementarity of the two strands explained how a single cell could replicate, namely by separating the two strands and simultaneously synthesizing the complement of each. Then identical chromosomes could be passed on to each daughter cell.

The epochal discoveries of Avery *et al*, and Watson and Crick put biologists on one of the most exciting and productive pursuits in the history of science. What followed was the deciphering of the Genetic Code which is imbedded in DNA, still evolving knowledge of how cells read that code, of how cells reproduce, of how we develop from the union of one sperm cell and one egg to the complex creatures that we are, of how our complex bodily systems, including the nervous system, work, and increasingly, of how we inherit traits and fall prey to disease and decline.

Coincident with the end of WWII, and with the discoveries of Avery *et al* and Watson and Crick, the field of study called molecular biology was born. Those discoveries alone, however, did not give rise to molecular biology. For example the use of radioisotopes, which came out of World War II, played an independent and seminal role in establishing the new discipline because radioisotopes enabled researchers to trace the successive steps of a metabolic pathway in a living organism. But the newly

recognized centrality of DNA provided the roots, stem, and branches of biology up to the present.

DNA is like a long string of beads, in which each bead is an element of the genetic code. Since the determination of the sequence of those elements in human DNA, which occurred within the past decade, genetics has blossomed as a way to get at the root causes of both health and illness. Thus far, however, those studies have enlightened us about the multilayered complexities of biology and deepened our understanding of various diseases, but have made only modest contributions to the practice of medicine. As a matter of faith, if a scientist may borrow that concept, I believe that in time we will learn how to cure or alleviate at least some of our most dreadful ailments including cancer, neurological, and autoimmune diseases. There are already several forms of cancer whose treatment has been devised or improved by information from genetic studies.

Factors:

A previous talk here in the Intellectual Trajectories series identified four important factors: Family, Mentors, Timing, and Luck.

Influence of an older brother, and shadows of the great depression

When I was about 9 or 10 years old, I convinced my parents to buy me a chemistry set for Christmas. It was, of course, a plaything, but when I began to read about chemistry, I discovered that I could write the chemical formula for table salt. That led me to sugar, whose chemical formula, though it was a bit more complicated, could also be readily written. In that chain of curiosities, I wondered how living creatures or parts thereof could be represented chemically. There were two aspects to that curiosity. One was a simple curiosity about another way to describe material things: thus in place of English words I learned that there are chemical words. Then the latter have additional significance because they hold in them the secrets of chemical interactions which are the basis of all life, and I wondered what chemical interactions could tell us about the composition and workings specifically of human beings.

I was born and raised in the shadows of the Great Depression. Along the way, I learned that when I was an infant my father had lost his business and home, and had been reduced to a modest level of earning power from which he never recovered.

When, in high school, I started to think seriously about my own future, I sought advice in my family. An older brother who had encouraged my interest in chemistry was starting on a career in medicine. I told him about my interest in scientific research. He told me that I could do research in medicine, and if that wasn't successful, I could still find a rewarding career in the practice of medicine.

The time was mid 40's. In 1940, President Franklin Roosevelt had dedicated the building and grounds of what would become the National Institutes of Health in Bethesda, Maryland, and in 1944 a legislative act created the basis for the broad role of the U.S. Government in the financial support of biomedical research. Even if I had

known about the birth of NIH at that time, the boost it would provide for biomedical research was not apparent to a youngster wondering how he could get a stimulating job that would pay a living wage. I never second-guessed my brother's advice.

Harvard College

From 1948 to 1952, I was a student at Harvard College. After studying inorganic and organic chemistry, I took a biochemistry course taught by George Wald, a renowned scientist, and a brilliant lecturer who was later to become a Nobel Laureate. He worked on the biochemistry of vision. When Professor Wald lectured about intermediary metabolism, the process by which food is converted into energy and the building blocks of life, I finally glimpsed some answers to my question about what chemistry could tell us about living creatures.

When that course was over, I asked Professor Wald if I could work in his lab. He agreed, and I spent free time and summers for the rest of my years in college working there.

He introduced me to laboratory research, and was also a model mentor for lecturing and writing. When, after a few years, I had the makings of my first scientific publication, he suggested that I write the first draft. When it was done, I gave him my draft and returned some days later, expecting lavish praise. After all, I was only an undergrad and I had been excused from the required second semester of English composition.

Dr. Wald asked, "Charlie, did you write this?"

"Why, yes, of course." I replied.

"It's the worst thing I ever read!" he said.

We both laughed testimony to a strong relationship of mentor and student, following which I studied his superb writing style, which put me on the road to scientific literacy.

Dr. Wald was also very good about introducing visiting scientists to those working in his lab. One day he came around with Hans Krebs. Because I had taken Wald's biochemistry course, I thought of Krebs as scientific hero after whom a central part of metabolism is called the Krebs Cycle. I was at my desk, studying for exams, while an apparatus (Kjeldahl) I had built was steaming away on my lab bench, getting cleaned. When Wald introduced me to Krebs, I was stunned and tongue-tied, so I explained why I had built the machine that was steaming away. Krebs, it turned out, also didn't know what to say, so he asked me,

"Haf you run a blank?" (i.e. "have you run a control.")

"Yes", I replied.

I didn't add that running a blank was all that I had done or would do with the apparatus until exams were over.

Harvard Medical School and Internship at the Boston City Hospital, 1952-1957

My years in medical school and internship were a special period of my life. A medical education is broad, and at its best appeals to one's better instincts. As a student and an intern, I saw patients in their most vulnerable moments and I came to understand better the workings, good and bad, of our emotions. I formed some of my longest and fondest friendships, and met my wife to be, Natalie. We married and started to raise a family. I recall an official social event, where the subject of our first baby came up, and surrounded by professors including a chief of Psychiatry, I expressed awe at how much our newborn child had to learn. The psychiatrist rejoined that he was more impressed with how much the parents had to learn. He won. We learned.

NIH and the Research Associate Program, 1957-1959

During my internship I learned that NIH was initiating a training program in basic research for MDs. I jumped at the opportunity and was accepted into the first class of Research Associates. The program consisted of lectures on various aspects of biomedical research, and hands-on research conducted under the supervision of the leader of one of the many labs. Those leaders were the functional equivalents of university professors, and the trainees were the functional equivalents of graduate students. The program was a kind of PhD-lite, in the sense that it was less than half the length of most PhD programs and did not confer a degree. The trainees in that first class were an enthusiastic cohort, a number of whom went on to academic careers, two of them here at Yale (Fred Cantor and me).

My mentor was Dan Steinberg. His boss was Robert Berliner, who later was to be the Dean of Yale's School of Medicine, during the early part of my time here. Both were physicians. Dan Steinberg was a very smart and amiable guy. He set me to work determining where serum lipoproteins are made, a project that excited me because in those days you had to make many of the reagents yourself, and I learned for the first time how to use radioisotopes to tag proteins. And the project was successful.

As the end of my two-year appointment approached, I had a big decision to make, whether to return to more training in clinical medicine or to seek a postdoctoral fellowship for more training in research. I opted for the latter. A college classmate, who was already a post-doctoral fellow with Arthur Kornberg, urged me to apply for the same position. Another example of chance. Kornberg, also an MD, was a scientific giant, who had just discovered an enzyme, called DNA polymerase that used DNA as a template to make copies of that DNA. It was another epic discovery.

Stanford: 1959-1962

I joined Kornberg's lab in July of 1959, just after it had moved *in toto* to Stanford University to form the new Department of Biochemistry there. That year Kornberg was awarded the Nobel Prize. The excitement of that event and the three years that followed was palpable. It was a time of rapid change in the blossoming field of molecular biology, when many of the key players visited Kornberg's Department to talk about their exciting new findings.

It was also demanding. There was a 24/7 work ethic, and very high standards. When, early in my stay, I gave a presentation at the Departmental journal club, my very first sentence was challenged from the audience by a loud, "Who the hell told you that?" The rejoinder came from Joshua Lederberg no less, a Nobel Laureate who was the Chairman of Genetics at Stanford. Well, it was a learning experience.

For the first two years, I worked in Kornberg's lab on the seemingly magical synthesis of incomplete forms of DNA, which contained only two of the natural components of DNA. We were able partially to demystify that enigma. During my last year, I worked in the lab of Dale Kaiser, a more genetically oriented member of the Department. The experiments done with Kaiser provided the first evidence that the sequence of genes in a chromosome is co-linear with their counterparts in DNA.

Department of Human Genetics, University of Michigan, 1962-1967

In 1962, with generous funding from NIH, I started my first job as an assistant professor in the Department of Human Genetics at the University of Michigan in Ann Arbor.

With my training in biochemistry, and a little contact with genetics at Stanford, I started research on an enzyme called lambda exonuclease, which was made by a bacterial virus that I had studied at Stanford. I also began examining the effect on the enzyme of mutants in various genes in that virus.

Eventually, and in cooperation with several genetics labs, we were able to show that the enzyme in question was involved in genetic recombination, a process by which chromosomes exchange parts. Genetic recombination plays two vital roles in our cells, each of which contains two copies of 23 chromosomes, except for the germ cells, sperm and eggs, which contain only one of each pair of parental chromosomes. One function of recombination is to identify and pair identical chromosomes prior to their segregation into germ cells. Another vital function of recombination is to repair broken chromosomes.

The involvement of lambda exonuclease in genetic recombination set me to work on recombination. That was a combination of luck and timing since at that time few other biochemists were working on recombination, which was seen as too complicated and too infrequent per cell to be amenable to biochemical investigation.

Department of Medicine at Yale 1967-

In 1967, I was offered a job in the Department of Medicine at Yale, in an experimental program to offer training in basic research to younger MDs who were in clinical training here. There were five of us in that unit which included Sherman Weissman and Frank Richards. The Chairman of Medicine who hired me, Phil Bondy, is here tonight. I am grateful to him for the opportunity that he gave me, and I greatly value our enduring friendship.

I arrived at Yale at the beginning of 1968, after spending an interim sabbatical for eight months at the Pasteur Institute in the laboratory of Francois Jacob, who

shared a Nobel Prize for the Operon theory of gene regulation. It was too short a time to accomplish much research, but I did get more training in genetics, as well as acculturation in the French language and gourmandise. Soon after I arrived at Yale, Fred Richards offered me a joint appointment in the newly formed Department of Molecular Biophysics and Biochemistry. In 1979, Leon Rosenberg, then chairman of a newly formed Department of Human Genetics, offered primary appointments to Sherman Weissman and me.

In my research, I continued working on the relation of our biochemical studies to genetic recombination. A national meeting on recombination that I attended focused on the genetics of certain fungi, which were excellent objects for genetic analysis. I came home, however, realizing how little I had understood. On the way to remedying that problem, I wrote a review on molecular aspects of recombination, which in turn got me invited to a small and exclusive biennial meeting on recombination that was sponsored by EMBO, the European Molecular Biology Organization. During an afternoon off, I was seated on a bus across from two colleagues, Seymour Fogel and Mathew Meselson, who were absorbed in a discussion, when I heard Matt say, "Let's ask Charlie." The question was about explaining an apparent anomaly in fungal genetics. I offered two explanations, the second of which elicited interest, but further discussion called for a diagram on paper, which we couldn't produce on a bouncing bus. At an after-dinner session that evening, I was having difficulty listening to the talks, because I was still thinking about the question I had been asked and the diagram that was needed, so I made the diagram. Across the aisle from me was Meselson, who was also making a diagram. We exchanged our drafts, which were identical. That led to a "general model for genetic recombination" that we published. The model's heuristic value led to new experiments in many labs, new discoveries, and a new reigning paradigm that replaced the model that Meselson and I had proposed.

Many years earlier, another good friend, John Clark, had discovered a gene, *recA*, that was required for genetic recombination in a bacterium; but the *recA* gene also had other complex roles which clouded a clear understanding of its role in recombination. In 1978, again at a scientific meeting, I was stimulated by some new observations on the properties of the protein made by the *recA* gene. In my lab we had at hand the tools needed to test the direct action of any protein in a recombination reaction simulated in a test tube. We went home and succeeded in showing that *recA* protein enabled a single strand of DNA to recognize homology in a duplex molecule of DNA and to invade it, forming thereby a stable product. Non-homologous molecules, i.e. genetically unrelated molecules, did not work in that reaction.

From that time until my retirement in the fall of 2004, we worked to understand the mechanisms by which *recA* and related proteins worked their magic. At the end, I concluded that apparently dissimilar proteins are led to do similar things that are dictated by the structure and properties of DNA, the home base of genetic determination.

There is a postscript. After I retired, I continued to serve as one of the editors of the Proceedings of the National Academy of Science; and at the beginning of academic year 07-08, my former chairman, Richard Lifton, offered me the part-time job of Director of Graduate Studies for the Department of Genetics to replace a departing faculty member who held that post. The role of the DGS is to see that the rules and procedures for the PhD are followed, and of equal importance to serve as counselor and advocate for students in need. The latter part of the job was challenging and fulfilling.