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RETROSPECTIVE

Charles M. Radding: A love of science and art

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Charles M. Radding, a pioneer of recombination biochemistry, passed away on October 20, 2020, at the age of 90. Charles was a world-renowned scientist who made major contributions to the fields of DNA recombination and repair, in particular through his mechanistic studies of the RecA protein. He was a man of humor and warmth, and an eloquent and inspiring lecturer who had a profound influence on others in the field. Charles was married to his wife Natalie for over 65 years, and has three daughters and a grandson.

Charles grew up in Springfield, Massachusetts. He was the youngest boy of five, and had one younger sister. His parents, Morris and Sara Radding, came from Russia in search of a better life. Unfortunately, Charles was born and raised in the shadow of the Great Depression and his family lost their business and home. It was not an easy time. But Charles was lucky enough to receive a chemistry set when he was 10 and this encouraged his curiosity in understanding the natural world. He discovered that chemistry provided a way to describe material things, and that the chemical codes for salt and sugar opened the door to view compounds in a way that words could not. Even at that early age he was fascinated by the concept that chemical interactions underpinned the workings of the human body.

Encouraged by an elder brother, Charles decided to go into medicine and enrolled in Harvard College. He was fascinated by the lectures of George Wald, who later received the Nobel Prize for discoveries on the chemical and physiological processes of vision, and carried out undergraduate research projects in his laboratory during his free time and summers. Charles credited Wald with his introduction to laboratory research, and as his early mentor for lecturing and writing. It was there that he met his future wife, Natalie, at a picnic, in what was to become an enduring and loving relationship.

During his medical internships in 1956, Charles learned that the NIH was initiating a program for medical doctors that wanted to move toward basic research, and joined the laboratory of Dan Sternberg to work on serum lipoproteins. This was the beginning of the end for Charles and medicine, and later in life when asked why he left medicine behind to pursue a research career, Charles would joke "I left medicine for the same reason that I went into it: To save lives."

Charles M. Radding at a laboratory celebration. Image credit: David Keith Gonda.

An opportunity arose to join the laboratory of Arthur Kornberg at Stanford, a scientific pioneer who later gained the Nobel Prize for the biochemical synthesis of DNA in a test tube. Kornberg's laboratory was a magnet for ambitious young scientists wanting

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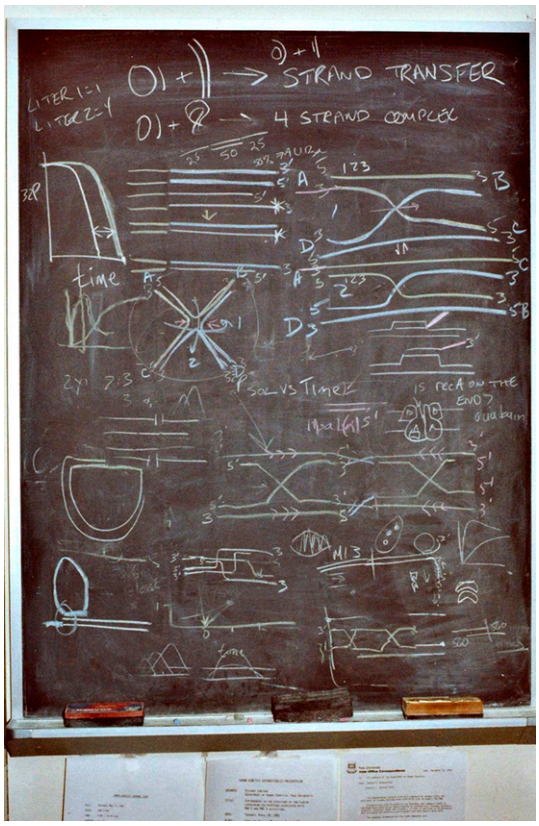

The blackboard in the Radding laboratory was a ripe source of new recombination models and mechanisms for how RecA might drive recombination. Image credit: David Keith Gonda.

to work on DNA in the exciting period after Watson and Crick's description of the double helix. Kornberg was a tough mentor who demanded a high-level work ethic and total dedication to research, but Charles survived and soon gained his own independent position as an Assistant Professor in Human Genetics at the University of Michigan. He brought his biochemistry skills to work on the phage lambda exonuclease, and discovered that this highly processive exonuclease produces single-stranded DNA that initiates recombination.

His first insights into recombination made Charles realize that here was a field that was effectively a blank page for an interested biochemist. For many years, recombination had been the realm of a highly intellectual group of geneticists, who built models to account for recombination based mostly on the products of fungal crosses. It also appeared to provide a means for the repair of postreplication gaps that arose in response to the incorporation of UV light-induced lesions in DNA. But to many researchers, the topic was simply too complicated to be amenable for biochemical studies, and no recombination genes had been identified at the time. The concept of a mechanistic biochemical approach to understand recombination was simply unimaginable.

In 1967, Charles took leave for an 8-month sabbatical at the Institute Curie in Paris to work with another Nobel prize winner, François Jacob. The stay was too short to achieve much in the laboratory, but Charles credits his stay there for improving his French language and the opportunity to discover fine food. He was remarkably talented at languages, and would happily give lectures in French to an amazed audience. He was so accomplished that many thought he had a Parisian accent.

Charles then moved his laboratory to the Department of Medicine at Yale University, who were kind enough to bestow him with an honorary doctorate in 1972. There he wrote a short review article on the molecular aspects of recombination, which led to him being invited to a European Molecular Biology Organization workshop that took place in Aviemore in Scotland. A traditional highlight of the meeting was an afternoon outing to the highlands for some hiking. On the bus trip, Charles was seated near Seymour Fogel and Matthew Meselson, who were deep in discussion about how current models for recombination, such as the Holliday model, failed to account for an asymmetry that was observed in fungal crosses. They invited Charles to comment, but the discussion needed pen and paper to draw a diagram, and the bumpy highland roads did not cooperate. Later that evening, however, neither Meselson nor Charles could focus on the after-dinner session, and instead were busy making drawings. After a while they exchanged their attempts at finding an explanation for the genetic anomaly, only to find that they had come up with nearly identical diagrams. The Meselson–Radding model, also called the Aviemore model, of recombination was born. Key to the model, which accounted for the observed asymmetry, was the suggestion that only one DNA molecule was nicked, allowing an invasion of one strand into an intact homologous duplex (to form a "displacement-loop" or D-loop).

At Yale, Charles set about finding biochemical proof for D-loop formation. In 1975, Bill Holloman in his laboratory showed that superhelical plasmid DNA could take up homologous single-stranded DNA to form a stable DNA heteroduplex in a thermally driven reaction that required only negative supercoiling. But how were these reactions catalyzed in the cell? Ten years earlier, an important advance came from John Clark's laboratory at the University of California, Berkeley by the genetic identification of a gene, *recA*, that when mutated led to a severe recombination deficiency in *Escherichia coli*. The biochemical function of the product of this gene was elusive, but Charles and his colleagues devised a clever experiment using bacterial spheroplasts to show that RecA was required for D-loop formation. The race to determine its role in recombination was now up for grabs, and Takehiko Shibata in the Radding group purified RecA and demonstrated the catalysis of D-loop formation in vitro. This was a remarkable time for biochemists interested in recombination, and the Radding laboratory was not alone in wanting to find out how homologous pairing took place. Indeed, over the next 5 years there was rapid progress in understanding the basic concepts of homologous pairing and DNA strand exchange

driven by RecA protein, through the studies of the Radding, Paul Howard-Flanders (also at Yale), and Robert Lehman (Stanford University) laboratories. It was a highly competitive period and occasionally tempers boiled over at conferences where whole sessions were devoted to report the new research findings on RecA. Charles knew that the knowledge being gained with RecA was important, not just for bacterial recombination, but also in humans. Later, when the human RecA homolog, RAD51, was identified and shown to promote essentially the same homologous pairing and strand-exchange reactions, his unparalleled insight was shown to be correct. That Charles published no less than nine *Cell* papers on RecA during this period is testament to the major contribution his clarity of thought, and elegant experiments, brought to the recombination field.

Aside from science and his linguistic skills, Charles was a lover of art, good music, and poetry. As a young boy he had a beautiful voice and sang in the community. Later in life he left it to others, but his love of the arts was never far away. In the 1990s Charles did a sabbatical at the Cancer Research UK laboratories in London. He was often found with Natalie on the South Bank listening to one of the many superb London orchestras. Indeed, his nickname "the culture vulture" was most appropriate, as he just couldn't get enough.

For his work on RecA, and contributions to our understanding of recombination, Charles Radding was elected to the National Academy of Sciences in 1995.

Acknowledgments

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