Charles M. Radding

1930–2020

BIOGRAPHICAL *Memoirs*

A Biographical Memoir by
Michael M. Cox

NATIONAL ACADEMY OF SCIENCES

CHARLES MEYER **RADDING**

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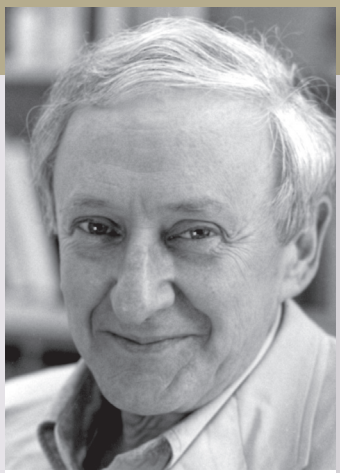

Charles M. Radding

By Michael M. Cox

Charles Meyer Radding was a prominent researcher who contributed major advances in our understanding of the process of genetic recombination and repair. He is best known for his work on the RecA protein and its role in cellular processes. In addition to his scientific work, he was also a generous mentor to those around him and an eloquent speaker and presenter.

As the Rakischik family gradually immigrated to the United States from Russia in the first decade of the twentieth century, an immigration agent anglicized their name to Radding. The event would uniquely identify this family tree. In later years, Charles Radding would relate that he always knew that any Radding he encountered was a relative.

Charles Radding was born in Springfield, Massachusetts on June 18, 1930, to Morris and Sara Radding, the fifth of their six children. Charles displayed some aptitude for sculpture early on. The gift of a chemistry set at age ten was even more influential. He learned that in addition to English words there were chemical words. Simple chemicals (table salt) and more complex ones (sugar) could be described chemically. Communicating with a brother serving in France during World War II, Charles revealed an early interest in the French language, presaging a later and deeper dive into French culture.

Charles attended college at Harvard University from 1948 to 1952. His interest in chemistry was strongly augmented and encouraged as he carried out undergraduate projects in the laboratory of George Wald. That introduction to laboratory research was a pivotal experience for the budding young scientist. The work Charles carried out in the Wald laboratory eventually led to three first author publications on rhodopsin and opsin.[1,2,3] The environment at Harvard offered much more. Charles encountered a continuous parade of visiting scientific notables, including Sir Hans Krebs and James

D. Watson. Biochemistry became a passion. In that rich environment, Charles became very much aware of one cellular molecule that had yet to win popular notoriety—DNA. Although DNA was hardly mentioned in his first biochemistry course, Watson's visit and his description of the two-stranded double-helical structure for DNA just proposed by himself and Francis Crick found a ready audience with Charles. Exploration of the literature uncovered the classic but then underappreciated work of Oswald Avery, Colin MacLeod, and Maclyn McCarty, making the importance of DNA clear. An enticing path seemed open, one that promised a greater understanding of the chemistry of life.

Following in the footsteps of older brother and mentor Phillip, Charles continued his education in medical school at Harvard. Phillip had assured him that an M.D. could lead to a career in research. If that did not work out, he could always fall back on medical practice. His interview for medical school was a bit unusual. Charles' story about it, as related by former Radding graduate student David Gonda, is as follows:

> *Charles was slated to be interviewed by one of the Harvard Med School faculty. He arrived at the professor's office at the appointed hour and sat down, only to watch the professor at his desk studiously ignore him. Charles decided he should just wait quietly until the prof was ready to engage him. He found out later that instinct was dead on; the professor in question was extremely shy and socially awkward. Trying to force him to engage would have been the worst thing to do. So he just waited. Charles said that after a few minutes of shuffling papers, the prof finally looked up and asked him "so, why do you want to attend Harvard Medical School?" Charles said he responded with the first thing that came to his mind: "well, it's close to where I live, and I heard it's good." Charles said that was the sum total of his medical school interview. The professor thanked him and ended the interview. And, of course, Charles was admitted.*

He completed his M.D. in 1956. As an important bonus of that period, Charles attended a picnic where he met Natalie, the woman who became his wife in December 1954. The relationship would endure for nearly seven decades and produce three children.

In a retrospective Charles wrote in 2009, he relates:

> *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 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, 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 the 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.

With medical school completed, Charles began a clinical internship. This lasted only a year, however. Charles' passion was elsewhere. He soon learned that the National Institutes of Health (NIH) was instituting a training program in basic research for medical doctors. Charles described it as a kind of "Ph.D. lite," taking half the time of a graduate program but conferring no degree. Mentored at the NIH by Dan Steinberg (also an M.D.), he took up a project to discover where lipoproteins are made. The work was successful and led to two new publications.[4,5] After the two-year appointment was completed in 1959, Charles faced another choice—go back to clinical medicine or pursue additional training in research. He chose the latter and never looked back. Asked much later why he took that path, he said: "I left medicine for the same reason I went into medicine: to save lives."

Charles next step finally steered his new research career to DNA. Encouraged by friends, Charles applied and was accepted as a postdoctoral researcher in the lab of Arthur Kornberg at Stanford University. He joined the Kornberg lab in July 1959, just after Arthur had moved the lab to Stanford and started Stanford's new Department of Biochemistry. Kornberg won the Nobel Prize that same year for his discovery of DNA polymerase. Charles remembers his years at Stanford as demanding. In one journal club presentation, his first sentence was challenged with "Who the hell told you that?" from Joshua Lederberg. Charles also was a witness to the birth of molecular biology at Stanford. He worked on DNA synthesis for two years in the Kornberg lab,[6,7,8] followed by a year of research in genetics with A. (Armin) Dale Kaiser.[9] The training in both genetics and biochemistry would serve him well in years to come.

In 1962, with funding from the NIH, Charles started up his own laboratory in the Department of Human Genetics at the University of Michigan. At the first, he worked on the exonuclease encoded by the bacteriophage λ, an enzyme he had begun to work

on at Stanford.[10] As this work progressed, it gradually became apparent that the enzyme had a role in genetic recombination.[11,12,13] This was an area of research that had, up to that time, been the intellectual province of geneticists. The reason was straightforward: the exchange of genetic information is a key process underlying the science of genetics. Recombination between chromosomes and the frequency with which it occurs allowed geneticists to discover and map genes. In organisms, particularly eukaryotes, recombination plays a role in creating and propagating genetic diversity. What other function it might have was obscure at the time. Biochemistry had yet to address it. Charles relates:

> *The involvement of bacteriophage λ exonuclease in recombination set me to work on recombination. That was a combination of luck and timing since at the 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.*

In 1967, Charles was offered a position in the Department of Medicine at Yale University. He accepted, but the move was delayed by an eight-month sabbatical in the lab of Francois Jacob at the Pasteur Institute in Paris. It was not enough time to get much research done, but it expanded his experience with molecular genetics. It also reinforced an interest in the French language, food, and culture that remained for the rest of his life.

Yale and Recombination Research

In 1968, Charles moved his laboratory to the Department of Medicine at Yale University, part of a new experimental program to teach basic research to younger medical doctors who were in early clinical training. Soon after he arrived, he was offered a joint appointment in the newly created Department of Molecular Biophysics and Biochemistry. The Department of Medicine conferred an honorary Ph.D. on Charles in 1972. Upon the later formation of the Department of Human Genetics in 1979, he was offered a primary appointment there as well.

At Yale, the Radding laboratory continued its exploration of genetic recombination, focusing initially on enzymes, particularly nucleases, derived from bacteriophage λ. After attending a national meeting on yeast recombination, he augmented his understanding of current research in the area by writing a review for the Annual Review of Genetics.[14] This in turn led to an invitation to attend and speak at a biennial meeting on recombination sponsored by the European Molecular Biology Organization (EMBO). A bus trip through the Scottish highlands on an afternoon off facilitated conversations with

Matthew Meselson and Seymour Fogel about then-unexplainable anomalies in fungal genetics. The discussion produced some ideas, but Charles and his colleagues could not create a needed diagram on a bouncing bus. Later, during the evening session, he found himself sketching out a model instead of listening to talks. Meselson, seated across the aisle, was also drawing models. They exchanged the drafts and found them identical. The model was subsequently published in the *Proceedings of the National Academy of Sciences* (PNAS) in 1975.[15] A key step in this and some other contemporary models was the creation of a single-strand break in one duplex followed by strand displacement to generate some single-stranded DNA. This single strand then went on to invade another duplex DNA. Although subsequent work led to its supplanting by the double-strand break repair model about eight years later,[16] the ideas in what came to be known as the Meselson-Radding model triggered much experimentation in labs around the world and helped to accelerate our present understanding of recombination pathways. The step involving a single strand invasion of a homologous duplex remains a feature of current understanding and this idea was to factor prominently in Charles' subsequent research.

Charles Radding lecturing on recombination in the early 1980s. (Credit Fay Radding Mascioli.)

Meanwhile, in 1965, A. (Alvin) John Clark had reported the isolation of mutants that affected recombination in bacteria, calling the first one *recA*. Although the *recA* gene was clearly important for recombination, the genetics of *recA* were very complex and suggested that its product, the RecA protein, had roles in multiple other cellular processes, particularly the SOS response to DNA damage and the mutagenesis that occurred during the SOS response. A regulatory function for RecA was possible and direct participation in recombination was not at all clear. Radding was watching these developments closely, but an "Occam's Razor" approach had him convinced initially that a protein should have a single function and that RecA must have some regulatory role. But the possible functions of the RecA protein were too interesting to ignore. By the late 1970s, the *recA* gene had been cloned (a process much more complex in that era than it is now) in multiple labs, notably by Kevin McEntee and Wolfgang Epstein at the University of Chicago[17,18] and by Aziz Sancar and W. Dean Rupp in Charles' own Department of Molecular Biophysics and Biochemistry at Yale.[19] The RecA protein was also purified by Cornell University's Nancy Craig and Jeffrey Roberts, who showed that it inactivated the bacteriophage λ repressor by cleavage.[20]

Charles at a lab celebration in the early 1980s. (Credit David Gonda.)

Radding, realizing that homologous recombination would require more than nucleases, was alert for any protein that might promote homologous strand pairing. Occam's Razor aside, RecA was on the list. At a meeting he attended in 1978, a talk revealed that the RecA protein had a single-strand DNA-dependent ATPase activity. Many at the meeting immediately saw the potential implications of this observation. Along with information he already had from ongoing work nearby in his own department, Charles was convinced that RecA was the protein he was looking for. His lab had already developed appropriate *in vitro* assays for recombination. He came home from the meeting and set his lab to work.

He was not alone. Kevin McEntee, completing his Ph.D. in the Epstein lab, took on a postdoctoral appointment in the lab of I. R. Lehman at Stanford and brought the RecA project with him. The biochemistry of RecA was also taken up by the lab of Paul Howard-Flanders at Yale. An intense competition ensued from 1979 to the early 1980s, with papers on the RecA protein appearing monthly in major journals.

The RecA protein wove a scientific spell that quickly entranced the field. The competition, initially involving the Radding, Lehman, and Howard-Flanders laboratories expanded rapidly during the 1980s to include more than a score of contributing labs worldwide. RecA protein formed long helical filaments that coated the DNA. Those filaments not only facilitated elaborate reactions involving multiple strands of DNA, they promoted the autocatalytic cleavage of the LexA and λ repressor proteins as part of the SOS response and also seemed to have some role in the mutagenesis that accompanies the SOS response. RecA seemed to redefine the term "multifunctional," as spectacular a failure of Occam's Razor as Radding ever experienced. For more than a decade, international meetings on recombination routinely featured major sessions focused entirely on the biochemistry of RecA protein. The discussion was sometimes heated but progress was rapid. The Radding lab had a central role throughout.

Pursuing Charles' major interest and building on his earlier recombination model, the Radding lab made an important early breakthrough. Radding's postdoctoral associate Takehiko Shibata showed that purified RecA protein would pair single-stranded DNA with homologous sequences in a duplex and invade that duplex to create stable D-loop

products.[21,22] RecA promoted the very reaction that Meselson and Radding had postulated several years earlier! The Radding group continued their seminal work on RecA in a series of influential papers published in *Cell* during this period.[23–31] RecA did much more than create D-loops. The dynamics and topology of complex reactions between homologous DNA molecules was followed and described. These contributions established the Radding laboratory as a leader of this now burgeoning field. As the exploration of RecA continued, understanding of its capacity to interact with, pair, and branch migrate DNA kept expanding. Continued advances saw the establishment of ever more complex *in vitro* assays, using DNA substrates that required skill and imagination to construct. The approaches used by the Radding laboratory, often elegant and always insightful, led to Charles' election to the National Academy of Sciences in 1995.

Charles at lab party in his home in 1991. Long sandwiches were a theme of these events.
(Photo source Takehiko Shibata.)

The main annual meeting in recombination, then and now, alternates between the United States and Europe. For more than a decade, the European venue was a small French chateau called Domaine Seillac in the Loire Valley. The location was fortuitous for Charles, facilitating visits to Paris before and after the meetings. The discussion of RecA continued during collegial dinners in Paris, often arranged by Charles, with science interspersed by his helpful explanations of the subtleties of the French language to colleagues who were novices in this realm. Good food was consumed while new initiatives and ideas were hatched. A wonderful lemon soufflé enjoyed in the 1990s at La Boule D'or comes to mind.

Charles, a superb biochemist who was always precise, rigorous, and highly competitive, remained a driver as progress continued into the 1990s. As the eukaryotic homologues of RecA protein were discovered, Rad51 and its meiosis-specific paralog Dmc1, the Radding lab expanded its efforts to include them.[32–39] The biochemistry of recombination rapidly expanded to include many additional proteins, a number of them with RecA accessory or regulatory functions. The Radding group generally remained focused on the intricacies of the reactions promoted by the central RecA-family recombinases. No aspect of RecA-DNA interactions went unexamined. The Radding lab was particularly invested in elucidating how homologous DNA molecules were brought together by

RecA—the homology search—and published extensively on this fundamental problem.[30,40–53] Although always intrigued and quick to offer suggestions and advice to colleagues, Charles sometimes seemed almost saddened as the attention of the field gradually focused on a wide range of additional proteins and away from the recombinases that had become his central passion.

As the end of the twentieth century approached, it was evident to many researchers that the creation of genetic diversity could not be the primary function of a cellular process that was being revealed as very resource intensive. Why would protein machinery of this sort evolve and be maintained in essentially all organisms? Work in multiple labs had shown that many genes had roles in both repair and recombination. All of this slowly congealed to reveal the answer to everyone: The primary function of recombination was to repair double-strand breaks as well as stalled or collapsed replication forks. The process had been hijacked by evolution to also play a key role in eukaryotic meiosis. This reality gelled for the entire field at a meeting in 1999, with Charles in attendance and contributing. To celebrate and further disseminate this major turning point in the field, Charles organized a conference entitled "Links between Recombination and Replication: Vital Roles of Recombination." Sponsored by the National Academy of Sciences, it was held on November 10-12, 2000, at the organization's conference center in Irvine, California. The meeting featured talks from forty-four prominent researchers and led in turn to a special issue of PNAS, published in July 2001. In his introduction to the issue, Charles addressed not only the past of the field, but also the increasing importance of recombination studies and their future:

> *Thus, to the classical view of recombination as an engine of inheritance we must add the view of recombination as a vital housekeeping function that repairs breaks suffered in the course of replication. We have also known for many years that genomic instability—including mutations, chromosomal rearrangements, and aneuploidy—is a hallmark of cancer cells. Although genomic instability has many contributing causes, including faulty replication, there are many indications that recombination, faulty or not, contributes to genome instability and cancer as well.*

Teacher and Mentor

Charles excelled as a teacher as well as a scientist. His lectures on recombination principles were especially sought out. As a graduate mentor, Charles involved his students in the social as well as the experimental aspects of science. His students routinely met and

discussed science with colleagues and visitors to the department, mirroring the enriching experiences Charles himself had benefited from as a student. At meetings, he was generous with introductions to other scientists and never insisted that students withhold information from other competing labs. Long discussions with competing colleagues were encouraged, and he would happily spend time in discussions with students from the labs of colleagues and competitors (an experience the author's lab regularly took advantage of). He was supportive but did not micromanage. He had a particular interest in the welfare of graduate students. Prior to his retirement, he served for periods as the director of Graduate Studies in the Department of Genetics. In this job, he viewed his role as advocating for the students rather than making sure rules were followed.

Charles finally retired and closed down his laboratory in 2004. Fittingly, the themes of DNA strand invasion and DNA pairing mechanisms were central to his final publications.[54,55,56] But Charles had a few more roles to play. At the request of the department chair, Charles came back for several years and served as the part-time director of Graduate Studies, where he found the role of counselor and advocate for students in need to be particularly fulfilling. He also served as an editor of PNAS from the time of his election to the NAS to several years after his faculty retirement. At his retirement gathering, then PNAS editor-in-chief Nicholas Cozzarelli remarked that Charles had set a record for the number of manuscripts he had carefully, rigorously, and fairly guided through the review process, substantially improving the quality of the Proceedings in the process.

Charles passed away in October 2020 at the age of 90, survived by Natalie, three children, and a grandchild. Charles was a consummate and dedicated scientist, esteemed and respected by colleagues around the world. He is greatly missed.

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