Donald M. Crothers

1937–2014

BIOGRAPHICAL *Memoirs*

A Biographical Memoir by
Peter B. Moore,
David Eisenberg,
and Jason Kahn

NATIONAL ACADEMY OF SCIENCES

DONALD MORRIS **CROTHERS**

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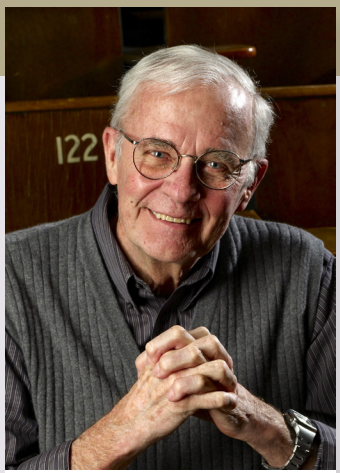

By Peter B. Moore, David Eisenberg, and Jason Kahn

Don Crothers spent his career studying the structure and physical properties of nucleic acids and the complexes they form with other molecules. In recognition of his many contributions to this field, he was elected to the National Academy of Sciences in 1987. In addition to being an outstanding scientist, Don was a gifted teacher whose wisdom was much appreciated by his students and research colleagues.

Don served his institution, Yale University, and its Department of Chemistry, with great distinction. He was chairman of the department for a total of 12 years (1975–1981; 1994–2000), and by the end of his career, his title was Sterling Professor, the highest honor that Yale can bestow on a faculty member. Don was also a successful scientific entrepreneur, a valued consultant to biotech companies, an author of monographs and textbooks, a loving family man, an avid appreciator of music, literature, and fine vintages, and a polyglot comfortable in German, French, and Finnish.

Early years

Don was born to Morris and Florence Crothers in Fatehgarh, India, where his father was working as a medical missionary for the Presbyterian Church. In 1939, the Crothers family returned to the United States; and in 1942, following his mother's untimely death and his father's remarriage, the family moved to Salem, OR, where Don grew up. His father, a practicing physician, was also a member of the Oregon state legislature for many years.

Don enrolled in Yale College in 1954. At that time, undergraduates who received financial assistance, as he did, were required to help offset the cost of their education by working for the university. The tasks assigned them were usually dull and menial, but not always; for four years, Don earned his keep by working as a research assistant in the

Department of Chemistry. He may have received this plum assignment because he had made it to the finals of the 1954 Westinghouse Science Talent Search.

The Department of Chemistry was a lively place in the 1950s, and Don's duties brought him into contact with many outstanding young scientists, among them Ignacio (Nacho) Tinoco, Jr., Stuart Rice, and Jon Singer, who later became his faculty advisor. Tinoco and Rice had come to Yale to do postdoctoral work with the department's chairman, John G. Kirkwood, a prominent theorist who chose biophysical chemistry/physical biochemistry as an area of emphasis for the department, which it has been ever since. Had Kirkwood not done so, Don too might well have spent his career elsewhere.

Don graduated from Yale in 1958 with a bachelor's degree in chemistry *summa cum laude* and shortly thereafter headed off to Clare College, Cambridge, where he enrolled as an undergraduate and read chemistry for two years. This venture was financed by a fellowship from the Mellon Foundation, which still runs a program that enables recent Yale graduates to study at Clare. By the time Don returned home in 1960, he had acquired a second bachelor's degree in chemistry, which some might think excessive, and a wife, which most would not. While on vacation in Paris between terms at Clare, he had met a Finnish pianist named Leena Kareoja, who was there studying music. The logistical problems confronting a resident of the UK intent on pursuing a young woman living in Paris, circa 1959, can only be speculated upon at this late date. Happily for Don, not only were these technical hurdles overcome, so too were whatever trepidations Leena might have had about living the rest of her life with him in the United States. They were married in 1960.

While at Cambridge, Don was admitted to the chemistry graduate program at the University of California, San Diego (UCSD). This was not as mundane a transaction as it might be today, given that UCSD did not formally exist when Don applied for admission in 1959; its official year of foundation would be 1960. The reason he chose UCSD instead of a more established institution was that Bruno Zimm had decided to join the UCSD faculty; and Jon Singer, who by that time had also decided to move to UCSD, had urged Don to get his degree with Zimm.

Don was USCD's first chemistry graduate student, a distinction that had some features a less determined individual might have found disconcerting. For example, Zimm's laboratory was a suite of empty rooms when Don arrived on the scene, and his first job was to order glassware. Such inconveniences notwithstanding, Don flourished at UCSD, and the research he did with Zimm set the stage for virtually his entire career.

By current standards, Don's passage through graduate school was breathtakingly swift. He was awarded his Ph.D. in 1963. Don and Leena then returned to Europe, where a postdoctoral position was waiting at Göttingen in the laboratory of Manfred Eigen, who was later to receive the Nobel Prize in chemistry for his studies of fast reactions. Only a year after their arrival in Göttingen, Don accepted the offer of a junior faulty position that had been extended to him by Yale's Department of Chemistry, and Don and Leena moved to New Haven. Though no records survive of the discussions that led to this offer, it cannot have been a hard decision for the faculty to make. Many of them already knew Don well enough to conclude that it would be good for the department were he to return.

Scientific career

Young scientists today are prone to believe that practically all problems regarding the structure of DNA were solved by James Watson and Francis Crick in 1953, but this is far from the truth. In the first place, for decades afterward, papers occasionally appeared in reputable journals that questioned the validity of double helical model for DNA; indeed, one of the authors of this essay (PBM) once heard Watson say that he had not been absolutely certain that the double helix was right until 1981, when Richard Dickerson and his colleagues published a 1.9 Å resolution crystal structure of a DNA dodecamer (1).

One of the many issues that remained unresolved when Don entered graduate school was the number of DNA molecules in a haploid chromosome. Is that number always one, as it seemed to be for the genomes of a bacteriophage, or are the much larger chromosomes of prokaryotes and eukaryotes assemblies of DNA molecules? For a polymer physical chemist like Zimm, the obvious way to answer this question was to measure the molecular weights of DNA molecules hydrodynamically, but that was/is much harder to do than it sounds. By 1960, there were many estimates in the literature of DNA molecular weights that had been obtained from measurements made in aqueous solutions.

Legend has it that while washing laboratory glassware one day, Zimm noticed that the rate at which beakers rotate in water solutions depends on viscosity. Inspired by this insight, he designed an ultra-low shear viscometer, which Don then built; and with some technical help from Leena, Don and Zimm went on to demonstrate how the viscometer could be used to estimate the molecular weights of very large DNA molecules (2, 3).

Don also collaborated with Zimm on some theoretical problems (e.g., 4) that Don continued pursuing after he moved to Yale. In an essay Don wrote on the occasion of

his 50th college reunion, he described the series of events that led him to conclude that he should devote himself to experimentation rather than to theory (5). A theoretical problem weighing on his mind had led him to an integral he was unable to evaluate, and after several days of struggle, he summoned up his courage and sought help from Lars Onsager, who was one of his senior colleagues. Onsager listened patiently as Don described what he was up to, and then had a look at the offending integral. After a few seconds, he said, "That will be a Hankel function of the second kind." (It should hardly need saying that Onsager was right.) If that was the level of mathematical sophistication required of those intent on a career in biophysical theory, Don reasoned, he would be better off doing something else. Thus, even though Don did return to theory every now and then (e.g., 6, 15), he is best known for his experimental work, much of which addressed the relationship between sequence, structure, and stability in nucleic acids; his interest in this relationship had been stimulated by his work with Zimm.

Over the years, Don's interest in nucleic acids' properties as a function of sequence took many forms. In 1973, in collaboration with Nacho Tinoco and Olke Uhlenbeck, he published a paper describing a set of rules—based on thermodynamic data the three research groups had accumulated—that could be used to estimate the thermal stability of RNA helices of known sequence (7). Years later, in a three-way conversation in which Don participated, Nacho told PBM that he had always referred to these rules as the "Crothers Rules," and Don replied that he invariably described them as the "Tinoco Rules." Whomever you choose to blame them on, these rules have since been refined and extended; their most recent versions account for the effects that phenomena such as non-canonical base pairings, terminal loops, and bulges have on the stability of RNA secondary structures, which the original rules did not. The predictions they now afford remain imperfect, but they are far more accurate than those provided by their initial version (see 8).

Intellectually, at least, the Rules were an important antecedent of a 1978 paper by the Crothers group on the lifetimes of the dimers formed by different species of tRNAs when their anticodon sequences can base-pair. The data were measured using the temperature-jump methods Don had mastered while he was in Eigen's group; and they spoke directly to the fidelity of translation, a problem that was then on many peoples' minds (9). At that time, the information available about error rates was sketchy, as it still is, and prior to the publication of Don's paper the Rules were the best tools available for estimating the free energies of codon-anticodon interactions.

Those data, such as they were, suggested that the translation system discriminates between cognate and near-cognate aminoacyl tRNAs far more accurately than the comparatively small differences in free energy between cognate and near-cognate anticodon/codon interactions would allow. This discrepancy had led John Hopfield and Jacques Ninio to propose (independently) that the translation system achieves its fidelity by exploiting those same small differences in free energy at least twice every time it selects an aminoacyl tRNA from the pool. Substrate-selection mechanisms that make this process possible are said to "proofread." Don's data proved unequivocally that the free-energy differences of concern were indeed as small as they had been estimated to be, and we now know that the translation system proofreads, just as Hopfield and Ninio had proposed.

Don's interests in nucleic-acid folding went beyond helix formation, as first became clear from the work he and his colleagues did in the 1970s on the effect of Mg^{++} on tRNA conformation, which is a tertiary structure problem. The issues they addressed in this larger arena included the structure and thermodynamics of bulges in DNA and RNA helices, the stabilities of different triple-helical structures, and the structure of intermolecular RNA kissing complexes. Don's work on these systems employed NMR, optical absorbance, and fluorescence methods, as well as biochemistry and molecular biology.

His appreciation of the interplay between structural transitions and ligand binding led to the realization that bulges in RNA helices can open up their major grooves, which are otherwise inaccessible, so that interactions can occur there that will result in sequence-specific recognition (10). Don's work in the dynamics of nucleic acids extended from the T-jump studies he and his colleagues did in 1970s to investigations of a riboswitch's mechanism of action. In the latter studies, he and Ron Breaker demonstrated that the rate at which a particular riboswitch functions is determined by its folding kinetics rather than by the thermodynamics of its folding (11).

In the early 1980s, the relationship between DNA sequence and structure reemerged as a theme in Don's laboratory in an entirely different guise. In order to understand what happened, it is important to remember that the Watson-Crick model for DNA described the average structure of B-form DNA. It qualitatively—not quantitatively—explained the underlying fiber-diffraction patterns. The Dickerson dodecamer structure mentioned earlier revealed the likely source of the quantitative shortcomings of the Watson-Crick model. The structures of DNA double helices vary along their length, depending on sequence, and one of the more astonishing manifestations of that sequence-dependence

was revealed by experiments that Don and his coworkers did on "kinetoplast DNA"—circular double-stranded DNA molecules, of modest molecular weight, that are found in the mitochondria of trypanosomes.

The Crothers group demonstrated that linearized kinetoplast DNA molecules are intrinsically bent (12). The group showed in particular that these molecules contain many short runs of oligo(A_n)•oligo(T_n) sequences, that each such sequence imparts a small bend in the helix axis, and that the separations between these "A tracts" in kinetoplast DNA are such that their bends add, imparting a significant overall curvature to any DNA in which they are embedded (13). Don later developed an elegant method for assaying bending effects of sequences; the technique took advantage of the fact that bent DNAs cyclize at rates that differ significantly from the rates at which unbent DNAs cyclize (14). Cyclization remained a focus of the Crothers group right to the very end; in 2003, Don his colleagues published an elegant analysis of the statistical mechanics of the DNA cyclization reaction (15).

So far, we have said little about another major theme in Don's research—the interactions of nucleic acids with other molecules. In some of these studies, the molecules of concern were small molecules that inhibit the capacity of DNA to act as a template for its own replication or for RNA synthesis; the molecules do this through insertion between adjacent base pairs—i.e., by "intercalation." The two types of intercalators that Don's group studied most were the actinomycins, which consist of phenoxazone rings that usually have oligopeptides appended (see 16), and the daunomycins, which are derivatives of anthracyclinone (see 17). Both classes of compounds are colored, which made assays straightforward. Don and his coworkers measured all of the relevant binding constants and off-rates, and they showed that intercalation at any given site in a DNA molecule reduces the probability that a second intercalation event will occur in the immediate neighborhood. They also showed that intercalation has dramatic effects on the physical properties of DNA, including its specific viscosity.

The number of proteins that bind to nucleic acids is very large, and the biological significance of the resulting protein-nucleic acid complexes is profound. It is not surprising, therefore, that Don published many papers on the interactions of proteins with both DNA and RNA, only three of which will be mentioned here. The first (which turned out to be Don's most highly cited paper) described a study, carried out using polyacrylamide gel electrophoresis, of the interaction of the lactose-repressor protein with a DNA containing its operator sequence. Don and others had already shown that the electro-

phoretic mobilities of nucleic acids change when proteins bind to them; these changes are called "gel shifts." What Don and his student Mike Fried showed in this study was that accurate estimates of binding constants could be obtained by analyzing the results of gel-shift experiments quantitatively, and, under favorable circumstances, that off-rates could also be measured (18).

The second paper, based on an extension of the bent kinetoplast DNA story, showed how changes in the electrophoretic mobility of bent/curved DNA could be used as an assay for bend position; it also reported the discovery that binding of the catabolite gene-activating protein (CAP) to its target DNA sequence makes that sequence bend toward the protein (19).

In an elegant follow-on paper (the third paper mentioned here), Don and his collaborators went on to characterize the bending induced by CAP binding in great detail (20). A few years later, Thomas Steitz and his coworkers published a crystal structure for a CAP-DNA complex that confirmed that CAP does indeed bend DNA (21).

Donald Crothers, 2003. (Family photo.)

Don as a mentor

Don's 67 former Ph.D. students recollect with remarkable consistency what life was like in his group. His insistence on the utmost rigor in experiments—and, especially, in their interpretation—was complemented by his extraordinary patience and generosity with students, who sometimes had to struggle to keep up with him. Don was renowned for the speed with which he grasped new experimental results, their significance, and the steps that needed to be taken next. For example, at a group meeting one day, when Mike Fried presented his early results on Lac repressor, which Don had not previously seen, his response from the back of the room was, "I don't know if you realize it yet, Mike, but your thesis project just changed." Sometimes students would tell Don about the results of their latest experiments one by one, hoping that by so doing, they would be able to give him the punch line before he saw it himself.

The fact that only 21 percent of the Crothers papers listed in PubMed have more than three authors reflects Don's practice of limiting the number of students working on any given project to no more than two. This gave each of them enormous freedom

and responsibility, and he was unusually good at meeting his students wherever they happened to be intellectually. Once, when asked how he always seemed to know what best to advise students, Don said that when we were as experienced as he had become, we would know how to do it also. This statement was simultaneously the kindest, and the most inaccurate, thing he ever said.

The atmosphere of Don's lab was all about intellect and integrity rather than bluster, aggression, or ownership. Thus it was always as welcoming for women as it was for men, and he treated women fairly and equally long before this practice was either commonplace or expected.

Life outside the laboratory.

There was much more to Don's life than teaching and research. First and foremost, he was a family man. Daughters Nina (born in 1965) and Kristina (1970) came on the scene during Don 's first decade as a faculty member at Yale. In addition to taking care of Don and the two girls, Leena pursued an active career in music both as a performer and a teacher, and, happily, her musical gifts were passed on to her daughters. The family made it a practice to spend a part of every year in Europe, including stopovers in Finland.

Leena and Don in Florence, Thanksgiving, 1998. (Family photo.)

Later in life, Don proved to be a devoted grandfather, ever ready to attend recitals, do science experiments, and play hide and seek with his grandchildren.

Somehow, in addition to managing his academic career and functioning as paterfamilias, Don found time to write three books. The first was a monograph on the physical chemistry of nucleic acids, which he coauthored with Victor Bloomfield (who had also been a Zimm student) and Nacho Tinoco. Many years later, in 2000, the same trio published an extensively revised and updated version of this treatise. During his first term as department chair, Don teamed up with UCLA's David Eisenberg, an old friend, to write a textbook on physical chemistry, which then was widely used for many years.

In 1982, Don embarked on an entirely different kind of venture. He and two Yale faculty colleagues, Frank Ruddle and Vincent Marchesi, founded a biotech company called

Molecular Diagnostics. Being one of the first Yale faculty startups, its launch was resisted by the university's president, who thought that the cost of the damage such enterprises might inflict on academic purity outweighed the potential intellectual and financial benefits to the university and the surrounding community. (Decades earlier, the rise of the government grant system for supporting faculty research had been greeted in New Haven with similar dismay, for similar reasons.) Molecular Diagnostics was financed by Bayer at a site, a few miles west of New Haven, that was owned by a Bayer subsidiary; the site now belongs to Yale. Molecular Diagnostics, and a second company called Molecular Therapeutics, which Don also helped organize, were bought out by Bayer in 1992.

As Don's second term as chairman drew to a close, his patience with university politics and general academic life was ebbing, so he sought other opportunities. From 2000 to 2005, he worked half-time as the chief scientist of GeneOhm, a biotech startup based in San Diego, CA. Because he was also running a research group at Yale, his commitments necessitated numerous cross-country flights. Don's life became a little less hectic in 2003, following his retirement from the faculty, but his schedule remained strenuous as he continued supervising research activities on both coasts. GeneOhm was bought out in 2006, and shortly thereafter Don began advising a venture capital firm based in Boston. He enjoyed working on the problems that these companies' activities brought to his attention, and for their part the companies' managers thought very highly of Don's advice.

In closing, we observe that in the mid-1970s, Don served as chair of the NIH Biochemistry and Biophysics grant-review panel. We mention this small part of his life here because the way in which Don carried out the role was so typical of him. The most innovative and complicated proposals were invariably assigned to Don for initial review, given that his mastery of physical chemistry could be relied upon to spot both their promise and pitfalls. His assessments were persuasive not only because of the thoroughness of his analyses, but also because of his insistence that every applicant be treated fairly. The secrets to Don's success in this endeavor, as in everything else he did, were deep intellectual insight combined with honesty and personal integrity.

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