Paul M. Doty

1920–2011

BIOGRAPHICAL *Memoirs*

A Biographical Memoir by
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NATIONAL ACADEMY OF SCIENCES

PAUL MEAD **DOTY**

June 1, 1920–December 5, 2011

Elected to the NAS, 1957

By Richard L. Garwin and E. Peter Geiduschek

Paul Mead Doty was born on June 1, 1920 in Charleston, West Virginia, into a family of modest means, further diminished, a decade later, by the Great Depression. When he was 7 years old, the family moved to Chicora, his father's hometown, a small West Pennsylvania community located about 50 miles north of Pittsburgh. A determining event of his early life there was a post-Christmas gift of a chemistry set when he was nine (1). He became passionate about chemistry, setting up his own laboratory in a garden shed used as a washhouse, saving up money to buy chemicals, and learning what he could about chemical reactions from books and lab manuals. An often-told story of life in Chicora concerns his time at the small local four-room high school, which nevertheless offered all the standard science courses. The responsibility for chemistry fell to the basketball coach, who was more at home in his coaching duties. When it became clear that his pupil knew more chemistry than he did and was inclined to offer correction during class, Paul became the chemistry teacher. By the time he was 15, he had determined what he wanted to do with his life. More remarkably, he had also formed a reasonably realistic notion of what scientists do and what constitutes scientific discovery. In other words, he was something of a prodigy.

Upon graduation, Paul Doty enrolled at Pennsylvania State College. This cannot have been an easy decision in view of the family's financial limitations, but Penn State had no tuition at that time and few fees, and Paul managed to support himself at least partly with odd jobs on and off campus. The college had a strong program in its School of Chemistry and Physics; Paul gravitated toward physical chemistry and took more math and physics than would have been common at the time. He was also taken on by J. G. Aston, a physical chemist, worked in his laboratory, and completed a research project on the barrier to rotation about the C-N bond of methylamine that was published as his first paper, a short note in the *Journal of Chemical Physics* (2). Armed with an introduction and recommendation from his mentor, Doty explored possibilities for graduate training at Columbia, Harvard and Princeton. He chose Columbia, where Harold Urey, Joseph Mayer, I. I. Rabi, Edward Teller and Enrico Fermi were all teaching, and in the fall of 1941 he entered the Chemistry graduate program. The country was still nominally at peace when he arrived at Morningside Heights but science was mobilizing; Doty took and sat in on first year graduate courses taught by these giants of theoretical and chemical physics, but by the spring of his first year, all except Mayer had left. Mayer became his advisor for research, primarily on the electron affinity of bromine, published as three short papers that he submitted as his 14-page Ph.D. thesis.

From the perspective of his scientific career, perhaps the principal event of that first year of graduate school was the encounter with Bruno Zimm, a fellow graduate and Mayer student and fellow employee on wartime projects. One of these, headed by the physical chemist V. K. La Mer, dealt with smokes and may have prompted Zimm and Doty to first think about measuring light scatter. Around that time (about 1943), Peter Debye gave a lecture in New York in which he sketched out the proposal that scattering of light in solution by large molecules would provide a means to measure their molecular weights. Bruno Zimm built a (simple) light scattering photometer, and together Doty and Zimm began to flesh out the theory of light scattering from solutions of macromolecules (3). The first themes of Paul Doty's research were set.

The molecular weight distributions, dimensions and conformations of large molecules in solution

In 1943, Doty also met Herman Mark, who was assembling a program in all aspects of the science of polymeric materials at the Brooklyn Polytechnic Institute. Mark, an accomplished scientist and charismatic organizer, had the resources to offer Doty and Zimm their first faculty positions and they moved to Brooklyn around the end of the year, taking along Zimm's photometer. Samples of polystyrene were also available from Mark and measurements of their molecular weight were promptly reported (4). It was already clear that, for sufficiently large molecules (that is, with characteristic dimensions approaching the wavelength of the scattered light), the angular distribution of scattering would yield information about molecular shape. Further analysis showed that light scattering would also yield some information about the molecular weight distribution of polydisperse high polymers. Thus it was quickly appreciated that light scattering was a valuable addition to the armamentarium of methods available for the physical characterization of synthetic high polymers (Zimm, Stein and Doty, 1945). This was also a focus of Mark's Department of Polymer Science and it became the principal subject of Paul Doty's research for approximately the next five years. At the same time, a collaboration with Gerald Oster yielded a determination of the molecular weight of tobacco mosaic virus and an estimate of its length and rod-like shape (confirming what electron microscopy had indicated), the first molecular weight measurement of a biological macromolecule in solution by light scattering (Oster, Doty and Zimm, 1947).

By the end of his second year in Brooklyn, Paul Doty was determined to move on; he applied for and was awarded a fellowship from the Rockefeller foundation for the 1946-47 academic year, to be spent in England, at Cambridge. Having resigned his faculty position at Brooklyn before realizing that his fellowship was contingent on evidence of continuing employment, he quickly secured an appointment in Chemistry at the University of Notre Dame for his return (1).

Figure 1. Paul Doty with Leo Szilard (middle) and Cecil Powell (left). Photo taken at the First Pugwash Conference, July 1957.(22)

The war in Europe had ended only a year before and the long march to recovery from its devastation was just beginning. In England, food rationing continued, that year's winter was harsh and although Cambridge was physically unscathed, the grim legacy of war was evident everywhere. Nor had the year at the Department of Colloid Science, nominally with (Eric) Rideal, very much to offer, but Max Perutz had recently returned to Cambridge and to protein crystallography, William Astbury, a pioneer of protein and DNA fiber crystallography visited periodically, and Gordon Sutherland, a spectroscopist interested in peptides and proteins, as well as others, provided an orientation toward biological macromolecules. And, as throughout his life, the year provided the opportunity to make acquaintance and establish friendships – with J. D. Bernal in London, The Svedberg in Uppsala, the polymer chemists Charles Sadron in Strasbourg and J. J. Hermans in Holland, Frédéric and Irène Joliot-Curie and Paul Langevin in Paris. It was during the year in Cambridge that he appears to have formed the decision to turn his focus to biological polymers, doing what he had done before with synthetic polymers, that is, determine their properties in solution (rather than turning to crystallography). Barely returned from Europe to his new position at Notre Dame, Paul Doty received an invitation to join the Chemistry Department at Harvard. He arrived there in the summer of 1948 and remained for the rest of his life.

Foundations of molecular biology

Although some work on synthetic high polymers initially continued at Harvard, an immediate start was made on the physical characterization of DNA, focusing on molecular weight and characteristic dimensions in solution. The material for these early studies was purified from animal sources by a lengthy (and mechanically brutal) procedure. Different preparations had molecular weights not exceeding ~6-7 million; light scattering and, in subsequent measurements, hydrodynamic properties indicated a very stiff, coiling molecule. A sample with somewhat lower molecular weight led to the prophetic suggestion that long DNA molecules might be sensitive to mechanical breakage (Doty and Bunce, 1952) (5). Denaturation at elevated temperature was shown to involve a co-operative collapse to a more compact conformation (Rice and Doty, 1957).

Figure 2. Paul with George Beadle. Photo taken in 1964 on the occasion of being awarded an honorary degree from the University of Chicago.

Very soon after establishing his laboratory at Harvard, Paul Doty turned his attention to the synthetic polypeptides, as models of proteins, in an extended collaboration with the group of Elkan Blout, who was working at the Polaroid Corporation but had recently established a second laboratory at the Children's Cancer Research Foundation in Boston. Application of light scattering and hydrodynamic methods to solutions of poly-γ-benzyl-L-glutamate showed an extremely stiff polymer chain in a chloroform-dimethylformamide mixture, compatible with the dimensions of an α-helix, and a collapsed conformation in dichloracetic acid, anticipated to destabilize the α-helix (Doty, Holtzer, Bradbury and Blout, 1954; Doty, Bradbury and Holtzer, 1956). In accordance with theoretical prediction by William Moffitt, Paul's colleague and friend, it was shown that the helix-coil transition (of polyglutamic acid) could be followed by monitoring changes of its optical rotatory dispersion, and that the optical rotatory dispersion of proteins could be used to estimate their content of amino acid residues in α-helical conformation (Yang and Doty, 1957). Observation of the cooperative helix-coil transition of polyglutamic acid in solution prompted the terse comment that "the parallel with protein denaturation is obvious"(7).

During this period, Helga Boedtker, then a graduate student and later Paul's second wife and life-long scientific collaborator, tackled the characterization of the macromolecular properties and denaturation of collagen in solution. Combined analysis of light scattering, intrinsic viscosity, sedimentation in the ultracentrifuge, flow birefringence and osmotic pressure yielded a molecular model consistent with a three-chain, rigid native conformation and dissociation of its individual chains of unequal molecular weight upon denaturation (consistent with X-ray diffraction analysis of collagen fibrils and electron microscopy of collagen, notably by G. N. Ramachandran, A. Rich, Francis Crick, A. C. T. North, F. O. Schmitt and others) (Boedtker and Doty, 1956). At this point, denaturation, all of it involving helix-coil transitions, had been analyzed in synthetic single stranded polypeptides, in double stranded DNA, and in triple stranded collagen and shown to share certain basic features, notably co-operativity, resembling "a process of melting in a one-dimensional crystal" (Doty, 1956)(8), and Stuart Rice had written a statistical mechanical theory of helix-coil transitions as a part of his 1955 Ph. D. thesis under Doty's guidance (9). Notable contributions to analysis of the secondary structures and spectroscopy of proteins and polypeptides, with W. Gratzer, G. Holzwarth and P. K. Sarkar among others (Gratzer, Holzwarth and Doty, 1961; Holzwarth and Doty, 1965), continued to flow from the laboratory for nearly another decade, but the main principles had been established.

Figure 3. Paul with Francis Crick and (sitting behind them) John Maddox. Photo taken in 1993 at Cold Spring Harbor Laboratory.

The work with the synthetic polypeptides and helix-coil transitions had drawn wide attention, talented students and a succession of prominent visitors to the Doty laboratory, but it was the discoveries relating to the nucleic acids at the end of the decade that have had a truly transformative impact not only on biology but also on its offspring technologies. The analysis of DNA denaturation had brought several questions to attention: Would guanine-cytosine (GC) and adenine-thymine (AT) base pairs confer different physical properties on doublestranded DNA (for example, would GC-rich and AT-rich DNA differ in regard to thermal stability)? Was the denaturation of DNA necessarily irreversible, as it had been seen to be up to that time (in experiments exclusively done with material from animal sources)? If denaturation of DNA resembled a phase-like transition, might the search for reversibility resemble the exploration of conditions for crystallization (of proteins, for example), that is, close to the phase transition?

The arrival of Julius Marmur and Noburu Sueoka provided the key impetus to answering these questions. After obtaining his Ph.D. in 1951, Marmur had chosen successive postdoctoral studies of different aspects of bacterial genetics and physiology with R. Hotchkiss at the Rockefeller Institute (as it was then called), at the Institut Pasteur in Paris, and with W. Szybalski at the Waksman Institute. With Hotchkiss, in a classical bacterial transformation experiment, he had given a molecular interpretation of genetic linkage as the presence of two genes on a single DNA molecule. Sueoka came to Harvard bearing high-GCcontent Chlamydomonas DNA. The DNA of different bacteria was already known to have different proportions of GC and AT base pairs. Marmur and Sueoka, together with Carl Schildkraut, extracted and purified DNA from different bacteria and the analysis of this material yielded a succession of brilliant insights. With regard to physical properties, the thermal stability and buoyant density were shown to vary linearly with AT base pair content (GC base pairs making DNA denser and more stable to thermal denaturation) (Marmur and Doty, 1959; Sueoka, Marmur and Doty, 1959), findings that were quickly and widely applied in a variety of contexts. The transformative discovery was the revelation of reversible denaturation of bacterial DNA as a somewhat slow process favored at temperatures somewhat below the "melting" (thermal denaturation) temperature and requiring sufficient electrolyte to suppress the electrostatic repulsion of negatively charged DNA chains (Doty, Marmur, Eigner and Schildkraut, 1960; the companion paper, by Marmur and Dorothy Lane, showed that "renatured" *Pneumococcus* DNA also recovered its transforming activity).

The discovery of DNA renaturation involved several essential components: a belief that DNA strands did, in fact, separate upon complete denaturation despite failure to have seen this in earlier measurements of molecular weight by light scattering (a conflict that was only subsequently resolved (6)) but supported by other recent evidence; a recognition of the power of Brownian motion and conformational flexibility of polymer chains to secure sufficiently rapid exploration of complementary DNA sequence; the right material – in this instance, the use of smaller-genome bacterial instead of calf DNA (increasing the concentration of every individual DNA sequence in inverse proportion to genome size at any given weight concentration, i. e. ~1000-fold, and the rate of bimolecular encounter by the square of that); and exploration of conditions near those of thermal denaturation (akin to annealing). Fortune was also required to smile (on prepared minds): a solution of bacterial DNA left at an elevated temperature (fortuitously corresponding to the optimum for renaturation) during a long lunch secured the first indication of reversibility (1).

Figure 4. Paul and Helga Doty at their house.
(Photo taken in October 1985 by R. L. Garwin..)

The revolutionary implications of being able to explore nucleic acid strands for complementarity were appreciated immediately and widely. In the Doty laboratory, the degree of identity of DNA from closely related bacteria and closely related viruses was promptly examined (Schildkraut, Marmur and Doty, 1961) (10), establishing a direct and quantitative methodology to determine phylogeny. Ben Hall, Doty's recent Ph. D. student, showed that the rapidly turning over RNA synthesized in T2 virus-infected bacteria (*Escherichia coli*) is complementary in sequence to the viral and not to the bacterial genome (11). Applications to every aspect of the biology and biotechnologies of nucleic acids—to the study of evolution and gene function, to the detection of mutation and identification of infectious disease, to genome sequencing, and to the material science of DNA—have developed in a constant stream over the subsequent decades.

It was natural that the interest in DNA as a macromolecule would also extend to RNA. Here, the task was to select, for study, material that would be sufficiently well-defined, homogeneous, and obtainable in sufficient quantity for analysis by the then-current macromolecular methods (and to prevent its degradation by adventitiously introduced or retained agents of destruction such as the ubiquitously present ribonucleases). The choice settled on RNA extracted from liver ribosomes and the already studied tobacco mosaic virus; both were found to be compactly coiled macromolecules in solution with properties comparable to those of denatured DNA. The discovery of polynucleotide phosphorylase by Grunberg-Manago and Ochoa made possible the synthesis of RNA molecules of simple, or complex and random sequence. Jacques Fresco, who played a leadership role in the work on RNA structure, had previously worked with Marianne Grunberg-Manago on synthetic polynucleotides and a research visit by Grunberg-Manago also helped the laboratory to practice the craft of enzymatic polynucleotide synthesis (12). A remarkable synthesis of a large group of experiments analyzing the thermal denaturation of these materials by optical and chemical methods, with what was already known about the thermal denaturation of DNA, generated the canonical model of the structure of RNA: it possesses internal secondary structure, consisting of variable-length but generally short helical segments formed by base-pairing between close-by segments of the polyribonucleotide chain folding back on themselves. Those helical segments might be imperfect, with nonpairing purine or pyrimidine bases looped out. In this way, even polynucleotide chains of complex and random sequence can assume conformations with considerable helical content. Natural nucleic acids, on the other hand, might encompass more and longer or fewer and shorter as well as more or less perfect helical secondary structure according to requirements imposed by their diverse functions (Doty, Boedtker, Fresco, Haselkorn and Litt, 1959; Fresco, Alberts and Doty, 1960).

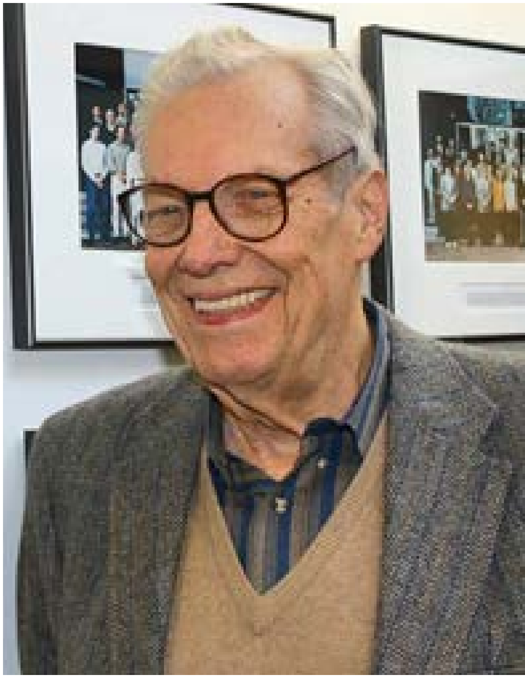

Figure 5. Paul at the Belfer Center.
(Photo taken in 2005 by Sharon Wilke at the Belfer Center, Harvard University and reproduced with permission.)

The 1961 Harvey Lecture provided the opportunity to present a synthesis of these discoveries (Doty, 1961) but it also marked a transition. Paul Doty was heavily involved in university affairs eventually leading to the creation of a Department of Biochemistry and Molecular Biology in Cambridge. He was increasingly involved in issues of public policy relating to nuclear armaments and the threat of nuclear war; he had become President of the Federation of American Scientists and a member of the inaugural Pugwash conference; and he was now appointed a member of President Kennedy's Science Advisory Committee. These activities, which are recounted in the next section of this memoir, were commanding increasing portions of his time and attention. At the same time, the laboratory was at the height of its power and reputation, continuing to draw outstanding students and gifted researchers. That momentum sustained the progress of research for more than another decade, but the nature and spirit of Paul Doty's involvement with it was changing. Up to this time he had been the essential determinant of its special character and the progression of its approaches to solving biological problems, its raison d'être. That changed now, gradually but progressively. He continued to guide, advise and critique, always incisively, but as the weight of his other concerns and obligations increased, the laboratory no longer retained his coherence of focus.

The work on the structure of RNA naturally turned attention to protein synthesis. When the startling experiment of Matthaei and Nirenberg on polypeptide synthesis directed by the synthetic RNA, polyribouridylic acid (polyU) was made known, it appeared to point a direct route to solving the Genetic Code. It seemed (13) that the laboratory's experience with the use of polynucleotide phosphorylase to synthesize RNA of varying composition made it ideally equipped to pursue the problem (along with others, of course). It turned out that speed was of the essence and, while the laboratory's work on protein synthesis contributed to understanding the direction of reading the genetic message (Thach et al, 1965) and to the initiation of translation with formylmethionine at the AUG codon (Thach and Doty, 1966), the principal contributions to elucidating The Code were made by others. Experience in making short oligonucleotides of defined sequence, which had accrued in pursuing the coding problem, did enable significant contributions to understanding diverse aspects of the dynamics of nucleic acid secondary structure formation and secondary structure stability. A notable example was the use of a small panel of tri- and tetra-nucleotides to probe the structure of the anticodon loop of initiator methionyl-tRNA and to demonstrate the ability of this tRNA to directly recognize and discriminate its conjugate codon without mediation by the ribosome (Uhlenbeck, Baller and Doty, 1970).

The decade following the Harvey Lecture saw the launch and later abandonment of several new research ventures, including interest in DNA inter-strand crosslinking by radiation and chemically, and the (possible) natural occurrence of such crosslinks in the cell; the specificity of antbody-antigen interaction; mRNA in the early embryo; and the structure of chromatin. Ultimately, sustained work on collagen was the consequence of Helga Boedtker's continuing interest in it, returning to the subject of her doctoral thesis. The determination of the structure of the chicken pro-alpha 2 (I) collagen gene was a major accomplishment of that work (Wozney, Hanahan, Tate, Boedtker and Doty, 1981): the most interrupted gene known at that time, with approximately 50 introns and many very small exons, encoding just a handful of amino acids. With a total length of approximately 38000 base pairs, not including its transcription regulating region, the pro-alpha 2 (I) gene would yield a primary transcript most (~87%) of which would be discarded in the process of generating the mature, translation-ready ~5000 nucleotide collagen mRNA. The final work on the subject bearing Paul Doty's name, published several years later, dealt with presumptive regulatory sequences of that gene.

The threat of nuclear arms: science and international security

On the occasion of Doty's 90th birthday, President Obama's greeting recognized Paul's:

> *work in bridging the Cold War divide to bring American and Soviet scientists together in pursuit of measures to reduce the danger of nuclear conflict.*

Indeed, Doty's contribution to world peace, understanding, and the prevention of nuclear war was phenomenal. He was an imaginative and assiduous worker in Washington, at Harvard, and, especially, in creating, nurturing, and maturing a relationship between American scientists and Soviet scientists influential with their governments and nuclear weapons establishments. During World War II, as a graduate student at Columbia, Doty had worked on experiments with heavy water at the beginning of the Manhattan Project. In 1953-54, he worked with the Technological Capabilities Panel (TCP), led by James Killian, of the Science Advisory Committee of the Office of Defense Mobilization. The TCP was formed in response to a direct request by President Eisenhower to understand the nuclear threat that could be posed by the Soviet Union to the United States and the possibilities for countering that by active defense or by civil defense.

Paul Doty was convinced that a major effort was required to bring the leaders of the Soviet Union and the United States to an understanding of the unacceptable threat posed by thermonuclear war, so in 1957, with his energy, open and friendly personality, drive, and work ethic, he served as chairman of the Federation of American Scientists (FAS). In July of that year, he was also one of 22 scientists present at the first meeting of scientists convened in Pugwash, Nova Scotia, by Cyrus Eaton, an industrialist from Cleveland, Ohio, in response to the 1955 Russell-Einstein Manifesto, which concludes,

> *...There lies before us, if we choose, continual progress in happiness, knowledge, and wisdom. Shall we, instead, choose death, because we cannot forget our quarrels? We appeal, as human beings, to human beings: Remember your humanity, and forget the rest. If you can do so, the way lies open to a new Paradise; if you cannot, there lies before you the risk of universal death.*

Doty was persuaded, through his contact with Soviet scientists at Pugwash, that there was an opportunity to work with these capable, intelligent people to begin to tame the nuclear threat through detailed discussion of the technical aspects of nuclear weapons, their effects, and their control, by scientists who, although at the time were not initially experts, could become so by serious joint study. The meeting in Nova Scotia was the first of the Pugwash Conferences on Science and World Affairs, of which Paul Doty was to be a leading member. He soon took the opportunity in those dark days of the Cold War to arrange with his Soviet counterparts to have a one-day meeting either before or after the international conference, a meeting of select people of the American and Soviet side to which other participants were decidedly not welcome.

Although U. S. participants were academics or occasionally interested and involved people from industry, the Soviets, naturally, were all employees of their government. The Soviet Academy of Sciences and the U. S. National Academy of Sciences were similar in name only – the NAS having been created in 1863 under a charter from the United States government, just as every U. S. corporation has a charter from one of the state governments, is an independent body. In contrast, the Soviet Academy of Sciences, with its proud background of achievement stretching back to its founding in 1724, was an element of the Soviet Union's government, in direct charge of the state's principal research establishments. Beginning in 1958, Paul Doty was to make 42 trips to the Soviet Union in his dedicated efforts to avoid nuclear war and to encourage informed cooperation between scientists on both sides.

Further, Doty became a consultant to the President's Science Advisory Committee (PSAC) in the White House, after it was formed in 1957 with James Killian as its first full-time head, and then served a four-year term from 1961 to 1964 as a PSAC member. Even after his time as a member, he remained a consultant until PSAC was disestablished by President Nixon in 1973.

Doty also played a key role in organizing a large Pugwash conference in Moscow in 1960, followed by one in the United States in 1961, which helped to set the organization on a firm and principled course of unofficial international discussions among scientists on problems not only involving nuclear war, but also concerning chemical and biological weapons, defense against ballistic missiles, and ultimately more general problems of people and society. Doty's competence, dedication, and energy, together with his personality earned him the respect and friendship of such leading Soviet scientists as Pyotr Kapitsa and Lev Artsimovich. Over the years, he formed, and co-headed from 1965 to 1975, the Soviet-American Disarmament Studies group (SADS) that was administered by the American Academy of Arts and Sciences. Doty's counterpart in SADS was M. D. Millionshchikov, First Vice-President of the Soviet Academy of Sciences. Henry A. Kissinger, Doty's friend and colleague at Harvard University, at times, also participated with that group, a connection that was important when Kissinger became National Security Advisor and then Secretary of State to President Richard M. Nixon.

Paul was a person of the greatest integrity and an inspiration to all those concerned with the arms control process. He kept notes of all of the meetings in which he participated and built upon them, but unfortunately did not get around to writing his autobiography. When Kissinger was selected by President Richard M. Nixon as National Security Advisor, it would have been natural for Kissinger and his national security staff to have reached out to the President's Science Advisor, physicist Lee A. DuBridge of Caltech, but the Nixon White House was a rather closed shop, and Nixon's aides H. R. "Bob" Haldeman and John Ehrlichman tried to limit inputs as much as possible, probably even from Kissinger. At that time, Doty and physicist members of PSAC Sidney D. Drell, Richard L. Garwin, and W. K. H. (Pief) Panofsky were concerned that crucial knowledge of science and technology, especially in regard to nuclear weapons, missile defense, arms control, and even the destructive effects of a nuclear exchange, was not well known to the White House. Despite competence in the Department of Defense and the nuclear weapons establishment, they considered it essential for the President and his senior staff to understand these matters "in their bones."

Paul Doty took the initiative to have Kissinger create a small, informal, personal, and sub rosa advisory committee, which typically met the day before or after the monthly two-day meeting of PSAC. PSAC occupied a large conference room in the old Executive Office Building, Rooms 206-208, but the “Doty group” would meet for an evening session with Kissinger in the White House basement situation room. Doty would lead the advisory group and Kissinger, of course, acted as the meeting chairperson. Notably, there was no staff present. In addition to PSAC members Doty, Drell, Garwin, and Panofsky, Jack Ruina, an electrical engineer who had previously served with Robert S. McNamara in the Kennedy/Johnson Pentagon, was also a member. Ruina’s MIT colleague and friend George Rathjens, with whom Ruina co-taught an arms control course at MIT, left the group after the bombing of Cambodia.

Figure 6. Formal portrait of Paul Doty, date uncertain but probably from the 1970s. (Bachrach Studios, Boston.)

Kissinger did not want it known that he was meeting with an outside group, especially with people who were well known in the technology and security community, so he arranged to have administrative support, travel funds, and clearances managed by Spurgeon M. Keeny, then Deputy Director of the Arms Control and Disarmament Agency (ACDA) housed in the State Department building. Position papers prepared over the previous months were briefed to Kissinger and discussed with him in the evening session. The next morning, the group would return to hear his response and would typically receive a new assignment for the next month. Among the topics discussed were those of ballistic missile defense, multiple independently-targeted reentry vehicles (MIRVs), and the structure of various arms control agreements.

In 1973, Doty began to organize annual Aspen Institute summer conferences in Aspen and Berlin on arms control, international security matters, and international science policy. The Aspen Strategy group later assumed this role, with Doty a member. Further, Doty was a member of the Executive Committee of the Dartmouth Conferences, which convened at regular meetings that brought together prominent citizens of the United States and the Soviet Union to discuss aspects of potential conflict and economic cooperation.

Seeking to expand and institutionalize the efforts being made in arms control and international security, Doty created the Program in Science and International Affairs at Harvard in 1973, as the first of several university research centers initiated with Ford Foundation support. In 1978, the Program evolved within the new Kennedy School of Government into a permanent Center for Science and International Affairs, which conducted teaching, research, and conferences. With support from the newly formed MacArthur Foundation, the Center began publication of its quarterly journal, *International Security*, in 1976 and Paul served as its founding co-editor (14). Doty served as Director of the Center from 1973-1981 and remained a Professor of Public Policy until his (obligatory) retirement in 1990. His activities during this time included serving as senior fellow of the Society of Fellows at Harvard (1963-1981), as a member of the General Advisory Committee on Arms Control (1977-1981) that advised the Secretary of State and the President of the United States, and as a member of the boards of Aspen Institute Berlin, the International Institute for Strategic Studies, and the Harriman Institute for the Advanced Study of the Soviet Union at Columbia University.

Doty's influence on international security was extended when the National Academy of Sciences (NAS) created the Committee on International Security and Arms Control (CISAC) in 1980 to meet semiannually with a counterpart group of the Soviet Academy of Sciences. Doty, Garwin, and Panofsky were among the founding members, with physicist Marvin L. Goldberger as CISAC chair. CISAC also published several reports on U. S. nuclear weapon policy and the U. S. - Soviet (now U. S. - Russian) nuclear security relationship. NAS Presidents Philip Handler and Frank Press played an essential role in the founding of CISAC. In 1988, CISAC began bilateral sessions with Chinese scientists and military officers of the Chinese Scientists Group for Arms Control, created within the Institute of Applied Physics and Computational Mathematics, a part of China's nuclear weapons establishment. Doty remained a CISAC member through April 1999.

Overall, Paul Doty's career has traveled down two distinct paths, academic research and the more political public policy avenue. Generally speaking, work in arms control and international security is quite different from scientific research. A scientific paper can change the world by giving a new perception, a new tool, or it can lay the basis for new technology. Even in science, not every revolutionary publication ignites a revolution and some of the most novel and far reaching discoveries may take a long time to be universally accepted. Work in arms control, on the other hand, more closely resembles work done in the public health sector or in education, either substantive or moral. It takes effect largely through persuasion, through expanding the ranks of the committed, and by educating new generations of military and political leaders in a way that helps them understand, accept, and recognize the necessity of what might be regarded as unnatural acts. These acts were unnatural in that they limit one's own capability with the goal of limiting the destructive potential of others in order to improve one's own security and, incidentally, that of the world. It is not only the magnitude of destruction that can be affected, but also the likelihood, and particularly the *stability*, of a potential confrontation. Thus, one should not look for blinding revelations in the publications cited here, but clarity, persuasiveness, and a basis for actions and commitment that largely benefits others, including the families, the compatriots, and the descendants of those who are persuaded.

In the 1991 *Daedalus* volume, Doty recounts the origins of modern nuclear arms control in the seminal 1960 issue, updating it to the time of writing, and projects another 30 years to 2020.

In his 1971 article in *Science*, he relates arms control and the search for peace to the community of science and scientists, who have played an outsized role in creating and advancing the progress of arms control through the worldwide nature of science, the mutual respect in which scientists usually hold one another (independent of political systems), and their ability to base discussion of potential threats and their solutions on this common background.

In a 1972 article, he addresses an aberration (one of several connected with ballistic missile defense) in the debate over U. S. defense against Soviet ballistic missiles.

In his 1999 *Nature* article, Doty reminds those who might be elated or relieved by the end of the Cold War that the nuclear weapons still exist and that the potential destruction, if they are used, would be vastly greater than that of WWII. He predicted that the level of devastation would even extend to the demise of civilization and the death of more than a billion people. Further, in a 2009 *Daedalus* article, Doty connects progress in reducing numbers of nuclear weapons, the preservation of deterrence against their use by states holding them, and the prospect for elimination of nuclear weapons and the consequent elimination of the ready deterrent against the use of nuclear weapons if they should covertly or overtly be rebuilt.

In that article, Doty outlines a path to minimum deterrence, but addresses the complication of a world in which at least eight nations must be persuaded and some people would argue that a nuclear deterrent must be maintained against biological attack or, in the modern day, even a cyber-attack. Russia argues that it is almost alone in a world of nuclear powers that are not always friendly to modern Russia. With more than 10,000 usable nuclear weapons at present in the world, perhaps only a major catastrophe involving these weapons can move nuclear powers forward along this path from the present status.

Beyond his publications in this field, Paul Doty's contributions to arms control and to national and international security lie in his influence on others to take up the cause and his direct and indirect persuasion of political leaders, ranging from President Eisenhower and President Nixon (through Doty's interaction with Henry Kissinger) to later generations, such as Senators Richard G. Lugar and Sam Nunn (especially through their interaction with Ashton B. Carter, Paul's disciple and now the U. S. Deputy Secretary of Defense). John P. Holdren, Science Advisor to President Obama, was Doty's long-time colleague in the Belfer School at Harvard and has a similar appreciation of arms control.

The importance of Paul's work in international security is indicated by the judgment of Evgeny P. Velikhov, prominent physicist in the Soviet Union and Russia, Vice President of the Soviet Academy of Sciences, and head of the Kurchatov Institute a key nuclear energy research and development institution. Regarding the newly established CISAC, he wrote (15):

> *Under the new U. S. administration of Ronald Reagan, it became virtually the only bridge of communication on issues of arms control between the U. S. S. R. and the U. S. A. (...) After the death of Inozemtsev I headed the commission on the Soviet side. From the U. S. it included such influential scholars as Marvin Goldberger (chairman), Paul Doty, Wolfgang Panofsky of Stanford, Dick Garwin from IBM, who designed the first U.S. hydrogen bomb some time ago, and several other scientists from the military-industrial complex. We agreed on priorities and chose the most acute problems threatening the mutual security of our countries: the cessation of nuclear testing, the threat of anti-satellite weapons, the deployment of weapons in outer space, and the ending of production of weapons-grade nuclear materials.*

Paul M. Doty's colleagues hold his contributions to U. S. and international security in high esteem, further reinforcing his accomplishments as an individual, as an inspiration, and through the institutions he founded and the people he influenced.

Legacy

Paul Doty has left a remarkable legacy of people, ideas and institutions. We close this memoir with a summary of the principal components of that legacy, to some extent recapitulating what has gone before. Many articles, obituaries, appreciations and celebrations of Paul's life have appeared in the past year-and-a-half. A selection of these personal tributes from former students and colleagues reemphasizes the sweep of his ideas and influence and allows other voices to speak for us.

The more than 150 undergraduates, graduate students and postdoctoral scholars who trained in the laboratory and shared in its discoveries are also an important part of Paul Doty's legacy to science. More than half have in turn become professors. They have made their own discoveries in a range of disciplines and a remarkable number have been recognized for their contributions by election to this academy, this country's other learned academies and sister academies of science abroad.

The more than 500 alumni of the Center for Science and International Affairs, which he founded in 1974 (now the Belfer Center, part of Harvard's Kennedy School of Government) are the people part of the Doty legacy in the area of arms control and international security. Many alumni have gone on to seed the systematic study of the interface of science and technology with public policy at other universities. Some have gone on to leadership positions in government and academia, including high office in the current administration of President Obama.

Paul Doty has been characterized as a serial institution builder. At Harvard, seeing the need for teaching and research at the interface of chemistry and the biological sciences, he successfully navigated treacherous academic currents to found, and brilliantly staff, a Department of Biochemistry and Molecular Biology in the Faculty of Arts and Sciences. In the area of arms control, recognizing the need to sustain the continuity of interactions initially largely dependent on personal rapport, he played an important role in institutionalizing these contacts by getting the National Academy of Sciences to establish CISAC, as already recounted in the preceding section. Seeing the need for training, sustained analysis and research at the interface of science and international affairs, he used his formidable persuasive power to establish the Belfer Center, as it is now called, with Ford Foundation support. And seeing the need for a journal to convey that scholarship, he established the Center's journal *International Security*, with MacArthur Foundation support.

Journals are central institutions of science and scholarship, often molders of opinion, determinants of what gets done and what remains unexplored. Doty was the founding co-editor of two other journals: the *Journal of Polymer Science* (with Herman Mark) in 1945 and the *Journal of Molecular Biology*, a premier venue of that field for its first decade (with John Kendrew as editor-in-chief) in 1959. That triad of chemistry, biology and international security epitomizes the remarkable range of his legacy.

Here are others writing and speaking about him

Walter Gratzer: (16)
Paul Doty was a great man. He made a mighty and beneficent impact in two quite disparate spheres of human endeavour. He prevailed in all that he set his mind to by dint of intellectual dominance, clarity of vision, and sheer force of personality. In science it was Doty more than anyone who brought physical rigour to the study of biological macromolecules when the spotlight shifted from metabolic biochemistry to the bright new discipline of molecular biology. The appearance in 1953 of the startling, if still conjectural, DNA structure, and the promise of protein structures to come gave a heightened purpose to questions of their size, form and behaviour in their natural aqueous milieu; this was the field that Doty bestrode like a Colossus for close on two decades.

Ashton Carter: (17)
Doty believed that national security affairs was important enough to human society that it warranted sustained and serious study, including in leading universities. He further believed that it ought to receive the rigor and peer review that he knew from the sciences. He therefore set out to found the "field" of science and international affairs and to give it the corresponding standards. The evidence that he succeeded is clear:

1) *He founded the journal* International Security, *a peer reviewed journal devoted to security issues, which is the leading journal in this field.*

2) *He founded the Center for Science and International Affairs at Harvard, which later became one of the principal ingredients of the new Kennedy School of Government. The Center's research, production of students and policy impact have been path-breaking and have served to catalyze the formation of a subfield at many of the nation's leading universities.*

3) *The U. S. Soviet Dialogues Doty established and maintained throughout the darkest days of the Cold War … can reasonably be said to have prevented misunderstanding that could have led to war, and (to have led to) the creation of ideas (many in the field of strategic arms control) that increased strategic stability. Equally important, when the Cold War ended, Russians who were part of Doty's dialogues were some of the first to populate the new government in Moscow, where they brought an understanding of strategy and American perspectives that prevented the new Russia from veering off in dangerous directions.*

John Holdren: (18)
Here is a man who has had a lifetime of accomplishment as a scientist-statesman, educator, policy-advisor, and institution builder at the intersection of science and international affairs – a career so full that it is hard to imagine how he found the time to do any science per se. You in this audience have already offered your judgments about his science. His monuments, from the other part of his career that it was my responsibility to cover tonight, include, in my judgment:

1) *The creation of the leading academic center of research and training on science and international affairs in the world;*

2) *The success of Cold War channels of communication between US and Soviet scientists that almost certainly were more important in averting catastrophe than any but a few will ever fully appreciate:*

3) *And in substantial measure the ABM Treaty itself, without which I really do think we would probably all by now be dead.*

Steven Miller: (19)
Paul Doty was a man of immense accomplishment: a world class figure in both science and public policy, a builder of institutions, an intellectual leader. Despite his stature, he was unassuming, almost self-effacing, and approachable. He rose high, but on his merits, because he seemed to lack almost completely the self-promotional instinct. There was no doubting his incisive, penetrating intelligence and his unerring ability to get to the heart of the matter. In a low-key, civilized way, he was full of intellectual integrity: no pandering, no backing down, no retreat from his beliefs in the face of high-powered opposition.

Matthew Meselson: (20)
The premise of Doty's approach to international security matters was that nuclear weapons are not for war-fighting or preemption but solely for deterring nuclear attack, the only role that might avoid their use entirely. Especially in the early years of the Cold War, this was by no means the settled view among senior officials on either side. Doty's influence on many who went on to occupy key positions in government and his leading role in the effort of U. S. and Soviet scientists to promote arms control must surely have helped to avoid catastrophe.

Bruce Alberts: (21)
In brief, Paul Doty founded the sub-field of "science and international affairs", endowed it with scientific rigor, populated it with talented people, and founded or co-founded its leading institutions. In this part of Doty's life, his "laboratory" was the Center he founded at Harvard and the other security-related institutions he nurtured. His "students" are the many high government officials and academic leaders he trained. His "break-throughs" were important ideas he and his "lab" contributed to strategic stability during the Cold War, to containing nuclear proliferation, and to providing solid scientific advice to Washington on a host of critical topics."

NOTES

1. Paul M. Doty, interviewed by Raymond C. Ferguson at Harvard University, 17 November 1986. Philadelphia: *Chemical Heritage Foundation, Oral Histor Transcript # 0062*. We are indebted to this account for information about Paul Doty's family and circumstances, and the early years, the physical and polymer chemistry phase, as it were, of his research career.

2. J. G. Aston and P. M. Doty Calculation of the heat capacity and entropy from spectroscopic data alone. The torsional mode of vibration. *J. Chem. Phys.* 8, 743 (1940)

3. B. H. Zimm and P. M. Doty The effect of non-homogeneity of molecular weight on the scattering of light by high polymer solutions. *J. Chem. Phys.* 12, 203 (1944)

4. P. M. Doty, B. H. Zimm and H. Mark An investigation of the determination of molecular weights of high polymers by light scattering. *J. Chem. Phys.* 13,159-166 (1945). *J. Chem. Phys.* 12, 144 (1944) is a preliminary report of this work.

5. The sensitivity of double-helical DNA to breakage by mechanical strain increases with the square of its contour length; entirely different methods were ultimately required to show that the chromosome of the bacterium Escherichia coli is a single circular DNA molecule, ~ 500 times longer than the average of those early DNA preparations. In fact, it was subsequently also realized (6) that light scattering, measured in the instruments then in use, had systematically underestimated native DNA molecular weights greater than ~2-3x106 .

6. J. Eigner and P. Doty The native, denatured and renatured states of deoxyribonucleic acids. *J. Mol. Biol.* 12, 549-580 (1965)

7. P. Doty, A. Wada, J. T. Yang and E. R. Blout Polypeptides VIII. Molecular configuration of poly-L-glutamic acid in water-dioxane solution *J. Polymer Sci.*. 23, 851-861 (1957)

8. P. Doty, J. Marmur and N. Sueoka The heterogeneity in properties and functioning of deoxyribonucleic acids. Brookhaven National Laboratory Symposium "Structure and Function of Genetic Elements" 1958, p. 1-15.

9. Not published until 1958, as S. A. Rice and A. Wada. On a model of the helix-coil transition in macromolecules. *J. Chem. Phys.* 29, 233-234. (The independently formulated theories of helix-coil transitions by B. H. Zimm and J. K. Bragg; L. Peller; T. L. Hill, J. Gibbs and E. A. DiMarzio; and J. Schellman should be noted.)

10. C . L. Schildkraut, Wierzchowski, J. Marmur, D. M. Green A study of the base sequence homology among the T series of bacteriophages. *Virology* 18, 43-55 (1962).

11. B. D. Hall and S. Spiegelman Sequence complementarity of T2 DNA and T2-specific RNA. *Proc. Natl. Acad. Sci. U.S.A.* 47, 137- 163 (1961).

12. Jacques Fresco has written an extensive account of his time with Paul Doty in *RNA Structure and Function*. Eds R. W. Simons and M. Grunberg-Manago,. pp.. 1-35. Cold Spring Harbor Press, 1998.

13. Personal recollection of R. Haselkorn, recounted with permission.

14. More precisely, Paul Doty was the Chairman of the Editorial Board while Albert Carnesale and Michael Nacht served as the Editors.

15. E. P. Velikhov Strawberries from Chernobyl. My seventy-five years at the heart of turbulent Russia (self-published at the CreateSpace independent publishing platform), S. Blees, editor, translated by A. Chakhovskoi) p. 177 (2012).

16. W. B. Gratzer Current Biology 22, R39-41 (2012). Walter Gratzer was a postdoctoral fellow with Doty from 1960 to 1963. He is a Professor of Biophysical Chemistry emeritus at King's College, London.

17. Quoted by B. Alberts at a Doty family memorial, recounted with permission. Ashton Carter is Deputy Secretary of Defense. He is the former Director (1990 – 93) of the Center for Science and International Affairs and Professor (on leave) of Science and International Affairs at the John F. Kennedy School of Government, Harvard.

18. Quoted by B. Alberts and recounted with permission. John Holdren is the Director of the President's Office of Science and Technology Policy and co-chair of the President's Council of Advisors on Science and Technology. He is a Professor (on leave) of Environmental Policy at the John F. Kennedy School of Government, Harvard

19. S. Miller Belfer Center Newsletter, spring 2012. Steven Miller is editor-in-chief of International Security, Director of the Belfer Center's International Security Program and co-chair of the U. S. Pugwash committee.

20. M. Meselson Science 335, 181 (2012). Matthew Meselson is the Thomas Dudley Cabot Professor of the Natural Sciences at Harvard.

21. Remarks by Bruce Alberts at a Doty family memorial and quoted with permission. Alberts was an undergraduate and Ph. D. student with Doty. He has served as U. S. Science Envoy to Indonesia and Malaysia, as President of the National Academy of Sciences, and is a Professor of Biochemistry and Biophysics emeritus at UCSF.

22. Powell was one of the original Nobel-laureate signers of the Russell-Einstein manifesto, and was heavily involved in the organization as well as the actual running of the conference that was held on July 7-10, 1957, at the Pugwash, Nova Scotia estate of Cyrus Eaton, the Canadian industrialist.

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