have been exceptionally fortunate to hold, as my only professional jobs, faculty positions at two outstanding research-intensive universities, the Massachusetts Institute of Technology (MIT) and Harvard University, for almost four decades. This has been an opportunity to work with many of the world’s best colleagues and predoctoral and postdoctoral students and to get an unparalleled and continuous education in the exciting scientific currents of this period. While at MIT, I had appointments in both the departments of chemistry and biology as my own personal bridging-biochemistry experience. At Harvard Medical School (HMS), in the biological chemistry and molecular pharmacology department for twenty-plus years, I have stood at a three-way intersection of biology, chemistry, and medicine in an institution with great basic medical science and twenty-six affiliated hospitals for expertise in any clinical medical specialty. I have taught undergraduates at MIT and Harvard in subjects ranging from organic chemistry to biochemistry and at HMS have taught biochemistry, chemical biology, and pharmacology to medical students and graduate students. What a remarkable set of opportunities!

Education

I grew up in Boston and, except for five years in graduate school in New York City, have spent all of my working life in that same location. I spent grades 7–12 at The Roxbury Latin School, founded in 1645, and that experience was the defining one for giving me the love of learning and the beginnings of belief that I could live the life of a scholar. The school was demanding intellectually, leading me, after some tribulation in the first two years, to good learning habits that served me well at Harvard College for undergraduate and The Rockefeller University for graduate studies.

I went to Harvard as an undergraduate in the fall of 1961, committed in an undifferentiated way to medicine, in part, I suspect, because my father worked for the pharmaceutical company Roche, and physicians were the success figures in his world. After being told in a freshman English writing seminar that I should look for another major, I gave up thoughts of writing seriously. (Although I note three books and more than 750 journal publications, perhaps to prove I am a contrarian.) I then became a biochemical sciences major until my last semester, when I switched to biology and took three courses required to fulfill the degree requirements. This switch was precipitated by the persistent denial of my petition for a waiver of the analytical chemistry requirement for biochemical sciences majors. I felt my three years of undergraduate research should qualify; the faculty were not swayed. The impasse came down to the final semester, but rather than give in (I suspect the analytical course in retrospect would have had value), I forewent biochemistry credentials at that stage. My choice of a faculty career has allowed me to deal with my authority problems by living in very autonomous “bottom-up” academic organizations.

While I was an undergraduate, two experiences rerouted me from medical school to graduate school. The first was a research project mentored by John Law in the chemistry department and
the famous biologist Ed Wilson on trail substance pheromones of the fire ant. The work, albeit only partly successful, like all research projects, turned into a first-author publication in the journal Nature (1). (It would be decades before I had another one!) The second event was that Konrad Bloch, whose laboratory space was adjacent to Law’s, won the Nobel Prize in Physiology or Medicine in 1964 for his deciphering of cholesterol biosynthesis. Research seemed like an exciting life path.

With letters from Bloch, Law, and Wilson, I was admitted to The Rockefeller Institute for Medical Research (now The Rockefeller University) in New York City for graduate studies in 1965. I was interviewed by the institute’s president, Dr. Detlev Bronk, who previously had been president of Swarthmore College. I did not fail to mention that my fiancé’s great-grandfather had been chairman of the board at Swarthmore. Bronk invited me to lunch in the university’s dining hall overlooking the East River, and I signed up. The medical research connection appealed to me, as did the fact that Rockefeller had ten times as many faculty members as graduate students and encouraged individual learning programs: no courses, no grades, but three comprehensive exams in major areas. I ended up taking those exams in biochemistry, physiology, and cell biology. The most enjoyable learning experience was a yearlong tutorial with three other graduate students, given by Professor William Agosta, in what I would now summarize as natural products chemistry. Although an unconventional substitute for graduate organic chemistry, it was active, not passive, learning, and it reinforced my chemical approach to biology and a pervasive fascination with the small organic molecules of life.

For doctoral research, I worked with Leonard Spector, then a chemically oriented associate professor in the laboratory of Fritz Lipmann (a 1953 Nobel Laureate), and started a career-long interest in the chemical mechanisms of enzymatic catalysts. I recall Lipmann as avuncular but painfully shy. He took notice of me a year into my affiliation with his laboratory when I published a paper on the mechanism of the ATP-dependent citrate cleavage enzyme (2). This is an enzyme discovered in his group a decade or so earlier as the cytoplasmic catalyst to generate acetyl-CoA molecules for lipid biosynthesis. The Lipmann laboratory was a remarkable microenvironment: famous co-workers who worked on unraveling the biochemical mysteries of B12. This project encouraged me to be independent (3, 4) and introduced me to mechanism-based enzyme inactivators, a focus on amino acid metabolism, and oxidation/reduction catalysis, all themes that were foundational in the first years of running my own research group.

Abeles and Bill Jencks had adjacent laboratory space at Brandeis and conducted joint group meetings on a regular basis. The combination of the deep mechanistic and sophisticated kinetic insights of Jencks and the wide-ranging intellect of Abeles to spot biochemical transformations where new chemistry would be unearthed had a deep impact on the approach I have taken to the study of enzymatic reactions: a chemocentric view of the reactions of life. After two years with Abeles, I looked for assistant professor-level academic jobs and was fortunate to receive multiple offers, the most intriguing of which was at MIT. After some complex and last-minute negotiations, I obtained a joint appointment as an assistant professor in both the chemistry and biology departments to start in the summer of 1972. My space and salary were the responsibility of the chemistry department, mostly to ensure that I did not have divided loyalties, but I had full access to graduate students in both departments, crucial, I thought, to
my research plans back when almost no one worked across those barriers (Fig. 1).

MIT

I recall on arrival at MIT wondering how I would ever attract a student or two to join my new group when they had the options of working with so many distinguished faculty members, including several Nobel laureates, in either the biology or chemistry department. One of the initiatives I took was to ask for approval to teach in my second semester a new graduate course on chemical mechanisms of biological transformations, called "Enzymatic Reaction Mechanisms." This initiative went against conventional wisdom to spend time on research rather than teaching. But the course, "Chemistry 5.50," which I taught every year I was at MIT, had twenty-five students the first time and averaged about forty to fifty students for the remaining fourteen years. Many faculty members sat in on the course in the first years. In short order, I had three biology and three chemistry graduate students, and the group was off and running, with enzymatic reaction mechanisms as the unifying agenda. Three years later, I had a research group of ten terrific co-workers.

One spinoff from teaching "Chemistry 5.50" was a 980-page book entitled Enzymatic Reaction Mechanisms, published in 1979 (5). This book encapsulated the philosophy of categorizing metabolism into a set of a few major types of chemical transformations, enabled by cofactors and coenzymes, to expand the chemistry available to enzyme side chains. It was for years a central resource for scholars in the chemical side of biochemistry and the biological side of organic chemistry and sold about 15,000 copies. It has been, appropriately, out of print for a long time. I have resisted impulses to write new editions, mostly because I do not think I would learn nearly as much as I did the first time; I like at least the illusion as a scholar that I am not backtracking, covering known ground, but spending time learning new things (and, see below, I have written two more books).

As the lab ramped up at MIT, we developed projects in mechanism-based inactivators of flavoenzymes and pyridoxal-P-dependent enzymes to explore the chemistry of latently reactive functional groups for those enzyme classes (6). We also worked out the stereochemical outcomes of several transformations at the β- and γ-carbons of amino acids during such pyridoxal-P-mediated transformations. One of the outgrowths was our study of the biochemistry of 1-amino-1-carboxycyclopropane, the immediate progenitor of the fruit-ripening hormone ethylene (7). Also, pseudomonads that live on leaves of plants can fragment that cyclopropyl amino acid to NH₃ and α-ketobutyrate, and we deciphered the mechanism and stereochemistry of that process (8). We also investigated the handling of several fluorinated metabolites/inactivators by enzymes to evaluate mechanism and stereochemistry, and this led us to inactivation of the enzyme alanine racemase by β-fluoroalanine (9), a molecule initially studied at Merck & Co. Blockade of this enzyme inhibits bacterial cell-wall assembly, and this finding triggered a long-standing set of studies into the enzymes that assemble the D-Ala-D-Ala-containing peptidoglycan layer of bacterial cell walls (10). This line of research intensified after the move to HMS in 1987.

A third early set of studies was on redox catalytic mechanisms of flavoproteins, including the study of 5-deazaflavin and 1-deazaflavin coenzyme analogs, initially enabled by a collaboration with Merck scientists (11). The 5-deazaflavin series (5-dFMN and 5-dFAD) was intriguing because the cofactor was now restricted to two-electron...
steps only, rather than the one- and two-electron pathways open to FMN and FAD. In effect, the 5-deazaflavins behaved as nicotinamide coenzymes embedded in a flavin framework. Among other things, this permitted determination of stereochemistry of hydride transfer to and from C5 and allowed characterization of the orientation of flavin/deazaflavins with respect to cosubstrates in flavoenzyme active sites.

The focus on flavoenzyme-mediated transformations led us into new areas of biology. One involved the microbial degradation of cyclohexanone into the acyclic carboxylic acid via an FAD enzyme-dependent ring expansion of cyclohexanone to the ring-expanded ε-caprolactone. This cyclohexanone monooxygenase was catalyzing a stereospecific and regiospecific oxygen insertion from O2 into a C–C bond of the substrate (12) and thus was the first well-characterized example of a biological Baeyer-Villiger reaction. A second initiative was an extended foray into bioinorganic metabolism, starting with an FAD enzyme involved in bacterial detoxification of mercuric ions (Hg2+) to elemental mercury (Hg0), which volatilizes out of the microenvironment. The mercuric ion reductase uses NADPH to reduce the bound FAD and then uses a relay of Cys disulfides to pass electrons from FADH2 out to Hg2+ coordinated to thiol ligands (13). We also studied the MerR protein in this degradative operon and characterized it as a metalloregulatory transcription factor where Hg2+ ligation altered affinity for Mer DNA (14).

Our work on 5-deazaflavin coenzyme analogs took a physiologic turn when 8-hydroxy-5-deazaflavin coenzymes, called F420s for their absorbance maxima at 420 nm, were discovered as redox coenzymes in such bacteria as mycobacteria and Streptomyces and in methanogenic archaea (15). This led us to purification and study of methanogenic bacterial hydrogenases that oxidize H2 and archaea (15). This led us to purification and study of methanogenic hydrogenases that oxidize H2 and

During that period, I also took on roles of increasing academic responsibility, perhaps initially inspired as utilizing problem-solving skills not totally divorced from the way strategies in research were planned and carried out. The last five years I was at MIT, I was the head of the chemistry department and enjoyed many, but not all, of the challenges such an office brings. It did give me an institutional perspective already bolstered by my full membership in two distinct academic departments. I briefly considered seeking the post of dean of science at MIT in 1986 but, in the end, chose to move to HMS and take on a different set of academic administrative responsibilities there.

**Pharmacology and Biotechnology I**

One set of activities that have been central to my knowledge base and to my philosophy of choosing scientific projects has been a career-long education in translational research and development. This started in my second year at MIT, in 1974, with a visit to Merck arranged by my chemistry colleagues. The longtime head of the department, the famous organic chemist Arthur Cope (of the Cope rearrangement), had been a stalwart consultant to Merck. Cope died just before I arrived at MIT, and the Merck chemists were open to visits by young MIT chemistry faculty. During my one-day visit and seminar in Rahway, New Jersey, I met with several groups of chemists, including a group working on fluoroalanine as an antibiotic that targeted alanine racemase. We had a lively discussion, as was true with other therapeutic area groups, and at the end of the day, T. Y. Shen, the head of the medicinal chemistry group at Merck, offered me a consultancy. It was the beginning of a seven-year stint at Merck. I like to think I made some useful suggestions, but I am sure I learned more than they did across an enormous range of therapeutic areas. Among the benefits of that relationship was the rapid development of my ability to listen carefully, to focus quickly, to summarize a complex set of observations, and then to make cogent suggestions and ask questions that seemed not to have surfaced previously: during this seven-year period, I became an effective consultant, the skills of which are highly transferable as a research director and in other settings.

We parted ways by mutual consent, as I became involved in the first wave of biotechnology startups, helping to found the immunotoxin/immunotherapy company ImmunoGen, Inc. ImmunoGen had great targets and strategies; it was just a couple of decades ahead of its time. Perhaps more notably, I was part of a group of seven MIT faculty members who were founding consultants to Genzyme Corp. We did three years of intensive consulting to
help shape the initial successful projects and then watched the company turn into a biotechnology juggernaut. I later did a ten-year stint as a consultant to Roche, both in the United States and in Switzerland, across a broad range of therapeutic areas. It appealed to me that my father, by then retired, had been a long-term Roche employee. I was even a consultant to a fragrance and flavors company in Switzerland; that was also a remarkable experience and a precious education in volatile natural products and their modes of biosynthesis.

Over time, I became known in the Boston scientific community, among academics and biotechnology scientists, as a resource about pharmacology and biotechnology issues, opportunities, and potential pitfalls. I have been careful not to exceed the one-day-a-week limit available to MIT and Harvard faculty members for outside professional activities, and I have never involved any of my laboratory personnel in company activities to keep a bright line of separation between my academic research group and any external consulting and board activities. The education I have received over thirty-six years of pharmacology and biotechnology consulting, watching what new ideas could be translated partway and occasionally all the way to new therapeutics, has been fully the equal of the ongoing education I have obtained at MIT and HMS.

**HMS and the Dana-Farber Cancer Institute: Academic Administration**

In 1987, I moved the research group all of 1.5 miles, from MIT to HMS, but the intellectual microenvironmental change made the trip seem across a substantially larger gulf. I think at least one move in a career is therapeutic, to start again in a new context and organization. It can break down encrusted patterns and can facilitate change in scientific directions. In my case, I also had harbored a continuing interest in medical research from the decision in 1965 not to go to medical school but instead to undertake medical research at Rockefeller. The MIT biology department was, and remains, superb, ranked at the top every year I was on its faculty, but in those days, it did not reach into human biology, pharmacology, or experimental medicine. There was no push to leave MIT, only the pull to learn more about therapeutics and human biology by going to/joining a medical school at age 43, in a nontraditional way.

I had been asked by the HMS dean, Dan Tosteson, to advise him on the future of the pharmacology department. I understood the surrogate nature of this role, and I also knew I was not the first to give advice, to be vetted by the dean, and to choose not to move to HMS. In retrospect, when the dean, one morning early in 1987, brought the conversation around to the possible combination of two HMS departments, biological chemistry and pharmacology, I think I was hooked intellectually by the prospect of such a bold organizational and intellectual initiative. Some months later, the HMS department of biological chemistry and molecular pharmacology was established, with me as founding chairman. The vision was to promote outstanding young faculty, hire structural biology experts in protein NMR and x-ray crystallography, and renovate the facilities. The dean was good to his word on all fronts. I got a crash course on chairing (from 1987 to 1995) a very different kind of department than the MIT chemistry department, as well as drinking from a fire hose of pharmacology, therapeutics, and many other facets of medicine in the first years at HMS. Of course, there were challenges in managing the merging of two academic departments that had no a priori desire to merge, but the quality of the faculty, the opportunities for promotions and new appointments, and the tincture of time helped. I taught both medical biochemistry and medical pharmacology courses for most of a decade, and that was a superb educational complement to the chemistry and biochemistry I had learned and taught at MIT.

I had good friends and colleagues at the Harvard-affiliated cancer hospital, the Dana-Farber Cancer Institute (DFCI). This led to the unanticipated opportunity to become president and chief executive officer of that 2000-person research hospital from 1992 to 1995. In that four-year period, I received a further education in both the administration of one of the nation’s leading cancer hospitals and the operation of translational and clinical science in cancer research. We ran a capital campaign, built new buildings, and dealt with the healthcare insurance turmoil of the early 1990s, but the three-part job of hospital chief executive officer, department chair, and principal investigator of a twenty-person research group was unsustainable. When DFCI was confronted with serious challenges on several fronts internally and externally in 1995, I realized that I was better at research than academic medical center administration and stepped away from both the institute chief executive officer position and the biological chemistry and molecular pharmacology department chairmanship.

Since 1996, after a thirteen-year period (1982–1995) as department head at multiple institutions, I have been in remission from academic administration. Nonetheless, the skill sets, including those four years of overseeing the complex institution that is the DFCI, have been useful both in my consulting roles to pharmacology and biotechnology companies as they face difficult decisions and in the
many advisory committees on which I have served within HMS, the larger realms of Harvard University, and advisory committees at the National Institutes of Health and the Howard Hughes Medical Institute. I worried in early 1996 whether I would be able to regain the original passion for scientific discovery as I got thirty to forty hours a week back from cessation of administrative duties. But, 350 papers and several new research directions later, I think the past decade and a half has been the best period of a long discovery career.

Pharmacology and Biotechnology II

Given the experiences detailed above, I continue to be truly interested in translation of laboratory discoveries into new medicines. This has led me to participate in several venture capital-based biotechnology startup companies in distinct therapeutic areas, both as a scientific advisory board member and as a board of directors member. These startups have included LeukoSite, Inc., which developed bortezomib into the front-line treatment in multiple myeloma, acquired by Millennium Pharmaceuticals, Inc., in 1999; Vicuron Pharmaceuticals, Inc., an infectious disease-focused company acquired by Pfizer, Inc., in 2005; TransForm Pharmaceuticals, Inc., a high-throughput formulations company, acquired by Johnson & Johnson in 2006; and Kosan Biosciences, Inc., which used natural product biosynthetic engineering for production of variants of epothilone and geldanamycin for cancer treatments, acquired by Bristol-Myers Squibb Co. in 2007. The acquisitions represented, in each case, a valuation of the innovative research and an increased chance for successful clinical development of the novel therapeutics all the way to United States Food and Drug Administration approval.

HMS Research

Most scholars are influenced by the currents of inquiry that swirl in the corridors around them. HMS has a different epistemology than MIT, although both are uniquely good at discovering new fundamental principles and truths and then applying them to important challenges in the real world. At HMS, my research group evolved over time from a graduate student-centered to a postdoctoral fellow-centered group, always in the range of fifteen to twenty outstanding, talented people. I am always looking for co-workers with whom I feel it will be fun and exciting to learn new areas of science.

One of the research foci that continued from MIT to HMS and got even sharper focus was antibiotics, both mechanism of action and mechanism of resistance. Over time, we also became driven to understand the chemical logic and biosynthetic machinery for the biosynthesis of naturally occurring antibiotics. Our work at MIT on alanine racemase and the next enzyme in the peptidoglycan biosynthetic pathway, d-Ala-d-Ala ligase, turned out to be a substratum for understanding resistance of bacterial pathogens to the antibiotic vancomycin.

From my time at the DFCI, I was aware in the early 1990s that vancomycin was often the antibiotic of last resort for the treatment of cancer patients who came down with life-threatening infections during cycles of chemotherapy when their white blood cell counts would cyclically be at a nadir. Patients who became infected with vancomycin-resistant enterococci (VRE) while they were immunocompromised were in a very precarious position. Fortunately, several of the antibiotics subsequently approved by the Food and Drug Administration act against VRE, but at the time, it was a pressing problem for which the mechanism of resistance was unclear. We were able to show that VRE had an alternate form of d-Ala-d-Ala ligase that used d-lactate in place of the second d-Ala, making the depsipeptide d-Ala-d-Lac (17). This could be incorporated into the peptidoglycan layer in place of d-Ala-d-Ala, and the bacteria could build a functional peptidoglycan layer. However, the d-Ala-d-Lac-uncross-linked peptidoglycan termini bound vancomycin 1000-fold less well, and thus, vancomycin could not achieve clinically useful levels to kill VRE (18). The absence of one hydrogen bond in the antibiotic-peptidoglycan complex was the difference between life (vancomycin-resistant) and death (vancomycin-sensitive) for the bacteria and, in certain patient populations, for the human host. The deciphering of the molecular basis of clinical resistance to vancomycin was one of the lines that got us thinking seriously about how vancomycin, a highly modified glycopeptide antibiotic, was produced by bacteria on nonribosomal peptide synthetase assembly lines.

A second convergent route to our developing program in natural product biosynthesis stemmed from investigations with Glenn Berchtold, an MIT chemistry colleague, on how the central metabolite chorismate was routed to a variety of aromatic products, including ortho-aminobenzoate (anthranilate) for tryptophan biosynthesis and para-aminobenzoate for folate biosynthesis, but also to isochorismate. In turn, isochorismate is transformed to 2,3-dihydroxybenzoate as the entry point to bacterial siderophore biosynthesis. In Escherichia coli, this siderophore is the iron chelator enterobactin with an estimated $K_D$ of $10^{-52}$ M for ligation of Fe$^{III}$. We worked on all of these enzymes branching from chorismate, but the most intriguing one was the processing of three molecules of 2,3-dihydroxybenzoate and of serine to form the cyclic...
trilactone enterobactin (19). We discovered that the enzyme EntF was active only if it had been post-translationally modified with a phosphopantetheinyl (PPTase) arm, the same prosthetic group found in the acyl carrier protein domain of fatty acid synthase (20). EntF, a 140-kDa protein, turned out to be a prototypic nonribosomal peptide synthetase module with four domains, condensation, adenylation, thiolation, and thioesterase in this order (21).

It took much effort to find the gene and enzyme (PPTase) responsible for post-translational phosphopantetheinylation, but when we did, this opened up a broad new avenue of research. We launched a full program into how the inactive apo-forms of nonribosomal peptide synthetases (NRPSs) were converted to the holo-forms modified with the phosphopantetheinyl group with its free SH group. This terminal thiol was the site where elongating natural product peptide chains would be assembled while covalently tethered (22). The conversion of apo- to holo-forms of thiolation domains by PPTase enzymes allowed coexpression in E. coli of heterologous NRPS modules and polyketide synthase modules in active forms such that the chemistry they carried out could be investigated systematically. In this line of research, my group was turning back thirty years and building on the pioneering efforts of Wieland Gevers and Horst Kleinkauf in the Lipmann group at Rockefeller in the late 1960s to establish the NRPS assembly line concepts.

Because siderophores are assembled by short NRPS assembly lines, it was possible to study the in vitro reconstitution with purified proteins from E. coli expression to generate enterobactin, yersiniabactin (from Yersinia pestis), vibriobactin (from Vibrio cholerae), and pyochelin (Pseudomonas) (23). Most siderophores are virulence-conferring factors, allowing pathogens to scavenge successfully in iron-limited host microenvironments. Understanding their biosynthetic logic opens paths to inhibition and attenuation of virulence. These studies were a prelude to examination of other more complex NRPS systems and also hybrid NRPS-polyketide synthase systems for bioactive molecules such as yersiniabactin, bleomycin, epothilone, andrimid, and others.

It has been possible to deconvolute the detailed mechanisms for not only the apo-to-holo priming steps of NRPS module activation but also monomer activation in chain initiation, peptide bond formation in chain elongation (including epimerization of L-residues to D-residues), and the various strategies in chain termination (including simple hydrolysis, macrocyclization to macroactams and macro lactones, as well as reductive release and subsequent reactions of the released peptidyl aldehydes) (24–26). The

macrocyclizations build in conformational constraints, are major determinants of potency in peptide-based natural ligands, and epitomize the maturation of peptide precursors into complex natural product architecture.

We have characterized many of the dedicated enzymes that accompany the mega-enzyme assembly line machinery to produce non-proteinogenic amino acid monomers, such as the hydroxyphenylgycines that are found in three of the seven residues of the vancomycin scaffold (27) and are responsible for the cross-links that allow that scaffold to be a high-affinity ligand for the N-acyl-D-Ala-D-Ala termini of bacterial peptidoglycan strands. Analogously, we have described many of the post-assembly line maturations that convert nascent inactive assembly line products into active antibiotics and antitumor agents. These include enzymatic N-acylations, iterative O- and C-glycosylations, and a variety of oxygenative modifications.

In the course of characterizing the cyclopropanation process in the phytotoxin coronatine, we turned up a novel class of non-heme mononuclear iron enzymes that act as cryptic halogenases (28) and halogenate unactivated C–H bonds by chlorine atom equivalents. In all, we have published about 100 research papers and half a dozen comprehensive reviews, which peel back the many layers of complexity and diversity from such natural product assemblages and collect a few common chemical principles for elaboration of simple building blocks into complex architectures. Among them is one entitled “Natural Products Version 2.0: Connecting Genes to Molecules” (33). Understanding the roles of domains in NRPS modules has given insights into assembly line evolution and how standalone NRPS modules sequester intermediates for oxidative chemistry in other pathways, as in coumarin antibiotic and dapdiamide antibiotic biosyntheses. This analysis also considers the NRPS assembly lines as molecular machines on the size of ribosomes (Fig. 2).

I wrote another two books during the past decade at HMS. The first is a monograph (29), **Antibiotics: Actions, Origins, Resistance**, providing a point of view on how antibiotics have evolved and how new ones might be found. The second volume is **Posttranslational Modifications of Proteins: Expanding Nature’s Inventory** (30). In some respects, this book originated from consideration of how phosphopantetheinylations fit in the pantheon of post-translational modifications (PTMs). It also represents a new framing of the 1979 enzymatic reaction mechanisms text (5) in the context of macromolecular proteins (rather than the small molecule substrates of primary metabolism) as substrates for common classes of enzymes, most of which catalyze transfer of electrophilic groups to
nucleophilic side chains in the proteins undergoing modifications.

Another class of PTMs we have studied in detail is the conversion of ribosomally produced proteins to bacterial microcins and antibiotics containing oxazole and thiazole rings that have been fashioned out of serine and cysteine side chains attacking the backbone peptide linkages. The thiazolyl peptide antibiotic class typified by thiostrepton and thiocillins may represent the apotheosis of PTM cascades. The processing of a 52-mer prepeptide to the mature trithiazolylpyridine scaffold of thiocillin antibiotics represents fourteen separate PTM enzymatic maturation steps (31).

Concluding Reflection

At the time of this Reflections article, my research group has been running for thirty-eight years. We have published the three books noted in this article and about 750 research publications and reviews. I could describe my predominant activity as writing, and that would not be incorrect, despite the abjurations of my freshman English professor. Mostly, I have written to explain the world to myself and thereby bring our research results into coherence, to find general lessons for how the chemistry of life is enabled from the particular findings of our research (32, 33). One of my M.D./Ph.D. students described my writing habits as hypergraphia, so it is nice to have a diagnosis.

The deep excitement of research has been continually enabled and unreasonably prolonged beyond what I could have expected by 80 doctoral students and 170 postdoctoral fellows throughout the years. That they have been spectacular scholars and great innovators is clear not only from the publication record but also from the great successes they have had in their subsequent careers.

I have taken my mentoring responsibilities as seriously as the discovery aspects of the scientific process, encouraging each fellow and student to pay great attention to the communication of their science. (As one index, more than 75 co-workers have gone on to academic positions.) I have felt there is a compelling chemical, biological, and medical story to be told about each of the research projects we undertook, and we should take that opportunity to make those lessons as accessible as possible to anyone who will listen and read. The learning dialogue from such co-workers, as we tell those scientific stories, has been an almost unimaginable education for me, as we have uncovered new facts and concepts together. As befits an enzymologist, my contributions have been catalytic.

Acknowledgments—I am indebted to the almost 250 graduate student and postdoctoral co-workers who have constituted the research group since its beginning at MIT in 1972. Their willingness to take on projects new to them and new to me has been a continuous thread of innovation as we have characterized more than 200 enzymes in primary and secondary metabolic pathways for novel and intriguing chemical mechanisms. I am also delighted to acknowledge forty-four years of marriage to my wife, Diana, a formidable scholar, public intellectual, and college president, who has been key in helping me grow into my scholarship through all these years. The research has been enabled by National Institutes of Health support, from both NIGMS and NIAID.

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