From the Bench to the Bedside and Back: An Essential Journey

Barbara Gilchrest, in her inaugural Editorial for this series on translational research, related that her clinical experiences kindled a desire to pursue laboratory-based training to bridge "basic discoveries at the cellular and molecular level with improvements in patient care" (Gilchrest, 2015). Her approach was bedside to the bench (...and back). My career had just the opposite genesis. I wanted principally to do fundamental biochemistry and cell biology and, indeed, embarked on a postdoctoral career studying tadpole metamorphosis under the tutelage of Arthur Eisen, then head of the Division of Dermatology at Washington University School of Medicine in St. Louis. That I found a career in dermatology, let alone one steeped richly in translational research, is due largely to consummately practical advice from two people.

Before I delve into the rest of that story, I want to set the stage. When she invited me to write an Editorial, Dr. Gilchrest asked me to review my career and the insights that fostered movement from fundamental research to academic administration and finally to industry. Reflecting on this challenge, I quickly realized that the assignment was not about *my* career, but rather about the plethora of challenges and opportunities that dermatology (writ large) offers to all of us. This commentary begins in the mid- to late 1960s, a scientifically fertile time for the deployment of nascent technologies, to bring them to bear on dermatologic diseases and to allow for observations that had theretofore been impossible.

Early in my postdoctoral career, one of the most stimulating descriptions of the scientific state of dermatology was offered in a 1967 *New England Journal of Medicine* review by Irwin Freedberg, then at Harvard Medical School and later chairman of the Department of Dermatology at New York University School of Medicine. In his article, entitled "Rashes and Ribosomes," Freedberg stated, "The era of the rash is in the past, and the era of complete understanding of dermatologic problems is still in the future" (Freedberg, 1967). Not given to unsubstantiated generalities, Freedberg cited as an example the importance of correlating recent electron microscopic insights with fundamental protein-synthetic and nucleic acid labeling studies to probe mechanisms of diseases such as psoriasis and ichthyosis. He reviewed the extant thinking about psoriasis to be the result of a process that "is genetically determined with a positive family history." He went on to say that, without proof, "I am certain that [psoriasis] is related to an abnormality in the control of either epidermal cell division or differentiation" and that data "have pointed to the existence of substances in skin ... that will control epidermal proliferation." His prescience joined that of perhaps a dozen others in dermatology at the time to adumbrate subsequent decades of work that have elucidated the complex genetic underpinnings of psoriasis along with a mind-boggling array of cytokine interdependencies that are keys both to the pathogenesis of the disease and to our hopes for rational interventions. At the time, such examples represented for me the excitement of being part of a discipline undergoing a metamorphosis from the descriptive to the mechanistic.

While the 1960s saw the blossoming of dermatologic clinical scientists deeply interested in the fundamental underpinnings of cutaneous biology, Freedberg (1967) used the "Rashes and Ribosomes" report to review how emerging techniques could also be used to understand therapy. He showed that when the widely used topical coal tar and UV light therapy (the so-called Goeckerman regimen) produced clinical remission of psoriasis, there was a concomitant fivefold decrease in DNA and RNA synthesis, as well as a significant decrease in protein synthesis, in the psoriatic plaques. Again, the excitement for me was the articulation of a collective sentiment, among an impressive array of dermatologic clinical scientists and skin biologists,

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that we were working at the dawn of a mechanism-based approach to fuel dermatologic therapeutics.

From our enlightened vantage point more than four decades later, we acknowledge—both intuitively and explicitly—that discovery of fundamental pathways will lead to better therapeutics. But acknowledgment also embodies a challenge: how do we maintain the flow of basic knowledge and what is the best way to ensure its translation into therapeutics? Now, as in the mid-1960s, dermatology remains ripe for innovation. Indeed, various waves of innovation have occurred over the past 50 years, including systemic and topical steroids for control of cutaneous inflammatory disorders; antimetabolites and immunosuppressive agents for control of psoriasis; systemic and topical antibiotics for the treatment of acne; systemic and topical retinoids for use in disorders of keratinization and in acne; novel forms of phototherapy, such as psoralen plus UVA and later narrow-band UVB, for amelioration of psoriasis and mycosis fungoides; calcineurin inhibitors for control of eczema; and biologics for the treatment of psoriasis. Each of these embodied the paradigm of bench to bedside to bench, as increasing efficacy and safety data impinged on product and/or regimen design. In a greater sense, as important as these advances have been to the lives of our patients, their emergence has been sporadic and stuttered at best.

My lifelong career conviction has been that maintenance of a flow of knowledge and discovery is crucial to survival, let alone a robust thriving, of dermatology. In 2000, I was deeply ensconced in issues related to payment for services in a major academic medical center. I argued that, despite the fact that—from an intellectual standpoint—dermatology had never been more exciting, much of the public and many payer organizations considered dermatology the study of relatively trivial diseases requiring little expertise and deserving minimal investment (Bauer, 2000). I further argued that public perception of dermatologists as aestheticians reinforced the very trivialization that we wished to avoid. In the intervening almost 15 years, little has changed to alter those perceptions. Let me emphasize that I in no way denigrate the need for dermatology and dermatologists to be responsive to the quality-of-life issues driven by patients' deep self-image needs. Rather, I argue that our value must rest on a solid scientific foundation and that we must, with one voice, articulate how science informs the needs—medical, surgical, and aesthetic—of patients.

Let me now return to advice given me by two wise mentors, both of whom counseled—not only with words but also by example. The first was Ruth Freinkel, who at the time was professor of dermatology at Northwestern University School of Medicine. As a medical student, I sought Ruth's advice about where to begin my laboratory research career. She could have urged me to stay at Northwestern, but with great generosity of spirit Ruth suggested that I go the Eisen lab at Washington University in St. Louis. The basis for her advice rested with the excellence of the science being done by Eisen and his collaborators, although I believe her more subtle goal was to ensure that I would be compelled by the excitement of doing real science as it related to dermatology. In retrospect, she could not have been more right, because the second role model was Arthur Eisen himself. What I learned from Arthur was multifold:

- To recognize the importance of the unity of science (i.e., genetic principles, protein-synthetic mechanisms, and regulatory controls transcend species and are, in principle, the same in bacteria, in amphibians, and in humans)
- To allow trainees to follow their noses scientifically and to provide a nurturing environment not excessively fettered by superfluous structure
- To encourage broad thinking and appreciation that the applicability of a technique used in a different discipline might apply to dermatology and that curiosity, tenacity, and common sense can pay off
- To develop a trusted team of basic and clinical scientists to engender cross-fertilization for optimal movement of projects—both basic and clinical—to fruition

These same principles have continued to guide me in my stints as department chairman, dean, and entrepreneur.

Perhaps the best example of a transition from fundamental research to industry is that of my first encounters with Genentech. During my Washington University tenure, our fundamental research involved connective tissue biology and biochemistry—synthesis and degradation of collagen—in health and disease. Inevitably, this led us (Jouni Uitto, then at Washington University, now chairman of dermatology at Jefferson Medical College, and me) to an interest in scleroderma and an examination of collagen-synthetic and matrix metalloproteinase expression in scleroderma fibroblasts. Our patient-oriented research was not truly translational; rather, it employed patient-derived cells to probe mechanisms (Uitto *et al.*, 1979). Upon my arrival at Stanford, Edward Amento, who at the time headed a connective-tissue/immunology group at Genentech, asked me to consider using recombinant human relaxin, an inducer of expression of matrix metalloproteinase I, as a possible therapy for scleroderma. We filed an investigator-initiated investigational new drug application with the US Food and Drug Administration (FDA) and treated one patient who suffered from moderately severe systemic sclerosis. The results were sufficiently encouraging to allow us (Amento at Genentech; Brian Seed, professor of genetics at Harvard Medical School; and me) to outlicense the relaxin technology and form our first company, at the time known as Connective Therapeutics and later renamed Connetics Corporation. We had come at least half-circle from bench to bedside. What we learned from later scleroderma patients would take us full-circle, i.e., from the bedside back to the bench. We learned that the amelioration of tissue fibrosis was seen in only some patients, and even in them it was not durable. The lesson was an important one—not to have tried would have guaranteed failure. To have tried for a solid-cell biologic/biochemical rationale at least informed future therapeutic avenues. Sadly, scleroderma remains one of the greatest challenges of dermatologists and rheumatologists.