Published in final edited form as:

Pediatr Neurol. 2018 March ; 80: 3–7. doi:10.1016/j.pediatrneurol.2017.12.002.

A Life at the Interface: The 2017 Hower Award Lecture

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What must it say about me
That my poetry is published in
Neurology?
I suppose it is better than if my
Science
Were published in
The Yale Review.¹

I have always seemed to get myself into these situations. I have long been seen as a poet by scientist and as a scientist by poets. I am a clinician to the scientists and a scientist to the clinicians; an oncologist to the neurologists and a neurologist to the oncologists. Mind you, I am not complaining. Among the most interesting and revealing phenomena are found at the interfaces between fields and sitting as “other” among “same” affords a unique view. Engagement in “interstitial enterprises” allows one to see connections one could not otherwise have seen and to find relevance in juxtapositions that are cryptic to most. Out of these interfaces come novel insights and constructs the applications of which are often difficult to predict.

There are, as well, many liabilities engendered in a life at the interface. One frequently feels like “The Man without a Country”², as those solidly in discipline “A” see one as being from discipline “B” and those in discipline “B” see one as being from discipline “A”. One finds oneself longing in vain for sympathetic reviewers, enthusiastic funding agencies, and even friends. Who else could possibly understand a string of seemingly unrelated observations viewed piecemeal? But it is all worth it when one day, one’s intellectual corpus is viewed in aggregate!

The narrative that follows, based on the 2017 Hower Award Lecture delivered at the Child Neurology Society meeting in October in Kansas City, MO, serves to illustrate the creative power of unique juxtaposition and the fruits born of “A Life at the Interface”.

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From Eastern Europe to Queens, NY

Right around the turn of the 20th century, my grandparents and their families made their way across the Atlantic to Ellis Island. Three-quarters of them came from Poland – Gostynin and Warsaw, to be exact. But, ever the anomaly, I am told I take after the other quarter. They came from Sadagora in Bukovina, Romania – now part of Ukraine.³ As with so many families, the oldest brother, Louis, came first and, as he earned enough money and got the paperwork completed, he brought his siblings – Josef, Harry, my future grandfather Nathan, Max, and Pauline – to America. (Of course, these were the American names they were given on Ellis Island.) Then Max went back to Sadagora and brought their parents, dubbed Samuel and Jeanette once they crossed the ocean, to the U.S. Fig. 1, a picture of Max and Samuel before they left Sadagora, makes what, for me, is a critical point. Max is a dapper emblem of the modern U.S. and century ahead, while Samuel is an icon of the old country and years past. Yet the facial features of the two men are almost identical. This juxtaposition of reverence for the past and creation of the future has been a guiding force in my life. We are all at the interface between what allowed us to be and what we will enable ourselves and those who come after us to become.

Love Unconditionally, but Watch Your Back

I have always thought of myself as a resonance hybrid of my two parents. My mother was the epitome of “unconditional love”. A semiprofessional singer and actress who made a living in the fashion industry in New York’s Garment Center, she had the gift of gab and an uncanny social sense. My father, as a result of what the McCarthy-ites did to his family, could never believe that the integrity or compassion of others was genuine. With his wickedly sarcastic sense of humor and his Ph.D. from Yale in chemical engineering and physics, he was the seeming antithesis of my mother. Together, they formed a synergistic whole and raised two daughters: an opera singer-music journalist who read complementary medicine journals and a physician-scientist who writes poetry and music. I owe my penchant for life at the interface to their example.

Baroque Fugues and Restriction Enzymes

Making music has always been a really important part of my life, from my first piano lesson at age 5 to atonal analysis studies with Allan Forte at Yale to my Pittsburgh debut as the keyboardist and singer with the Klezmer group, “The Hot Matzohs”. But the blatant juxtaposition of science and art came later and took a very different form. My undergraduate years at Yale afforded me the outstanding mentorship of three amazing biochemists. Lubert Stryer, Harold Morowitz, and Sophia Simmonds, each in their own unique way, took me under their wings and urged me out of my comfort zone. Towards the end of Freshman year, in cahoots with one another, they persuaded me that I should apply for the summer Undergraduate Research Program at Cold Spring Harbor Laboratories⁴, a program usually reserved for college Juniors and Seniors. I was accepted and spent the summer of 1973 in the laboratory of a very young Richard Roberts, now Nobel Prize winner Sir Richard Roberts, discovering and characterizing restriction enzymes.⁵

Restriction enzymes, made by bacteria, cleave DNA at palindromic sequences; the 5'-to-3' strand reads the same as the 3'-to-5' strand at the cleavage site (Fig. 2).⁶ Dr. Roberts viewed these restriction enzymes as tools, wonderful facilitators of the ability to sequence DNA fragments and piece the fragments back together to ultimately discern the mRNA for which it codes. Much to his chagrin, I was much more fascinated by the enzymes themselves as proteins. Imagine the geometry and stereochemistry of the enzyme's active site that enabled cleavage at such a symmetrical locus! This was truly art in nature.

In addition, that was the summer of the Watergate hearings.⁷ There I was, waiting for an agarose gel to run, Scientific Products, Inc. timer on my belt (so I could get back to the lab in time to see the tracking dye run off the bottom), sitting riveted in front of a big TV with Nobelists James Watson and Max Delbruck, and with Max's children, Toby and Ludina, playing with Lincoln Logs on the floor. On the screen, Halderman, Dean, Mitchell – they were all there. There I sat, at the veritable interface between science and the real world, as my idols learned that their idols indeed had feet of clay.

Structure and Function, Function and Structure

Through Yale's unique Scholar of the House program⁸, I spent my entire Senior year in the physical biochemistry laboratory of Julian Sturtevant. My choice of Sturtevant's lab came about because I just could not get the elegant match of enzyme form and function I had encountered at Cold Spring Harbor out of my head. I worked on the protein hen egg white lysozyme (Fig. 3)⁹, and it did not disappoint! I discovered that, although the active site and all of the disulfide bonds of the enzyme were remote from the N-terminus, if one broke the protein's disulfide bonds and cleaved off the N-terminal 10% of the molecule, the disulfide bonds reformed incorrectly (i.e., mismatching the cysteine residues) and the enzyme no longer worked. If one broke the disulfide bonds without changing anything else, one could get the disulfide bonds to reform correctly and the enzyme would work. Even the short stretch of protein that seemed to have nothing to do with its function was there for a reason. Its stereochemical and thermodynamic contribution to the enzyme held the active site in the right geometric configuration. It is indeed ironic that it took us many decades to learn that lesson again with DNA. So-called junk DNA isn't junky at all!

Another lesson I learned by the example of the Sturtevant lab bears repeating today. The lab included researchers and trainees from the U.S., Mexico, Turkey, the U.K., Canada, and Iran. The calorimeter we were privileged to use was a gift from Dr. Sturtevant's collaborator in the U.S.S.R., Peter Privalov.¹⁰ Our calorimeter had the serial number 00003. Numbers 00001 and 00002 were in Moscow. Mind you, this was 1973–1975, at the height of the Cold War.¹¹ Science happily overcame politics, language barriers, and national customs. The diverse human structure of Dr. Sturtevant's laboratory served and, indeed, enriched its function.

Rational Drug Design and Learning How to Think

As for many who have pursued child neurology as a career, for me, the choice of neurology was an intellectual one. I was fascinated by the complexity of the nervous system and the

fact that understanding its function required collaboration among scientists engaged in studies of anatomy, biochemistry, physiology, psychology, and even philosophy. The choice of child neurology, on the other hand, was a social one. I could think of no one with whom I would rather spend my professional life than children and pediatricians! So I started graduate school at Rockefeller University knowing I wanted to be a child neurologist and convinced that my PhD work would be in neuroscience. But I also knew that electrophysiology and behavioral science, the predominant neuroscience foci on the Rockefeller campus, were just not my thing. Especially when studied in squid axons and songbirds, respectively! I was a biochemist intent on using biochemical principles to design and test therapies for human diseases.

I opted to join the lab of biochemist and pharmacologist, Anthony Cerami, whose work involved determination of the biochemical underpinnings of disease and design and preclinical and clinical testing of pharmacotherapeutic agents aimed at those biochemical abnormalities. My PhD thesis work on the biochemical mechanisms behind the abnormal viscosity of the secretions of patients with cystic fibrosis led me from laboratory bench to animal facility to clinic to hospital as I studied sputum glycoproteins, putative mucolytic agent distribution in animal models, and changes in pulmonary function tests of patients with cystic fibrosis enrolled in my double-blind, placebo-controlled, crossover study of a novel putative mucolytic drug. I had the outstanding good fortune to do various parts of my project with a parade of amazing thinkers and innovators like Stanford Moore, Peter Blackburn, and Charles Peterson, and to meet some of the most resilient children and families and intellectually generous physicians in the CF clinics at Mt. Sinai Medical Center, Columbia Babies Hospital, and St. Vincent's Hospital. My thesis committee was chaired by Maclyn McCarty (of the famous Avery-McLeod-McCarty experiment¹²), one of the most humble and gracious individuals I have ever known. I learned, during those years, how to plan and think and bring ideas to fruition through analysis, collaboration, sequential logic, and lots of rolling with lots of unforeseen punches. I felt ready to apply those principles and strategies to the study of disease of the developing nervous system.

Defining a Unique Niche

While I went to medical school thinking I already knew I wanted to be a child neurologist, it was the attention paid to me by the Chief of the Division of Child Neurology at Cornell University Medical College, Dr. Hart de C. Peterson, that really clinched the deal. I had approached him very early in my first year at Cornell asking if I could do something that might give me a clear idea of what life as a child neurologist was really like. He immediately invited me to attend weekly case conference in his division. For the ensuing six years, every Friday morning before class or lab, I attended the sessions. It did not take long for the team, and especially the trainees who were not that much older than I, to think of me as one of them. What a heady experience for a new medical student!

My neurology clerkship was, completely by serendipity, scheduled to occur at Memorial Sloan-Kettering Hospital, with Dr. William Shapiro as my group's preceptor. Dr. Jerome Posner substituted for Dr. Shapiro when he was at a national meeting for a week. I confided in both that I was pretty sure I wanted to pursue a career in child neurology. One afternoon,

Dr. Shapiro said to me, “Neuronal tumors of children are what you should work on. Unlike the glial tumors of adults, they all have neurotransmitter receptors. Maybe you could attach a toxin to a neurotransmitter and make the neuroblastoma take it up!” We discussed this idea a bit more, and it was he who told me about 6-hydroxydopamine being used to destroy CNS neurons to create a model of Parkinson’s disease.

Somehow, I could not get that idea out of my head. As a pediatrics resident at Boston Children’s Hospital, I took my one month of elective time and set up a “reading elective” with Drs. David Nathan and Stephen Sallan as my mentors. We must have read everything written to that point about neuroblastoma! By the end of that month, I had written a research project proposal. Years later, as a neurology resident, I put all six months of elective time at the very end of my three years of child neurology training and got to initiate my project in the laboratory of Manfred Karnovsky, a man of great intellect, pedagogic and scientific skill, and humor. That was truly the beginning of a very long and productive effort to target neuroblastoma for therapy and leave normal, developing tissues unscathed.^{13,14}

From Autism to Alzheimer and Back Again

The science I have pursued has led me to one overarching conclusion: that, whether you are an infant or child or adolescent or adult or elder, it’s all about development. The notions that one end of the spectrum is called development and the other end is called senescence and that there is a discrete line at 18 or 21 years of age that separates the two are absurd! Not only is there no conflict in the simultaneous study of development and aging; one informs the other because they are part of the same continuum. The molecular and biochemical evidence for this is compelling, indeed.

For example, my lab’s work on neuroblastoma, a developmental tumor of the primitive sympathetic nervous system, led us to study and define the biology of the neurotrophin receptor, p75NTR. So when a post-doctoral fellow in the lab next door to mine told me she wanted to work with me on Alzheimer disease because presenilin is one of the gamma-secretases that cleave p75NTR, allowing its intracellular domain to go off to the nucleus as a transcription factor, I listened even though I am a child neurologist.^{15,16} Several years later, I realized as a result of those Alzheimer disease studies that p75NTR expression goes from ubiquitous in the prenatal brain to predominant expression just in the cerebellum and hippocampus in the adult. I wondered what might happen if it disappeared in those loci, too, as one developed and aged. My colleagues and I knocked out p75NTR only in the granule cells of the cerebellum of mice and produced mice with many of the characteristics of human autism.¹⁷ The child is indeed father to the man!

The Value of Balancing Work and Life

My professional life to date has taken me and my family from Boston to Pittsburgh to Rochester. This career at the interface has borne fruit at the expense of sleep, food, vacations and weekends, social occasions with friends, and witnessing all of my children’s daytime early life explorations first hand. Professionally, it has often meant that no one else speaks a

complete version of my language or even cares about it. My “professional family” and the family of my professional pursuits were never one and the same. So why was it worth it?

To be sure, there are unique insights borne of odd juxtapositions. There are new approaches that shed new light on old and hitherto intractable problems. But what truly makes it all worth it are the people you engage as mentors, the people with whom you are mentored by them, and the people they empower and equip you to mentor. There is honestly nothing quite like the continuity and legacy engendered in grasping a baton from someone, changing it and shaping it uniquely, and passing it on to someone who you know will do the same. As I begin to come full-circle so that many of my former “mentees” now teach me as much as or more than I taught them, I am reminded of the graciousness of the luminaries of science and industry who, in 1972, presented to me the national first prize in the Westinghouse Science Talent Search. At the time, I thought they were just being incredibly nice even paying attention to a 16-year-old high school kid. But maybe they felt as I feel so often now, passing a changed baton to someone they know will change it yet again.

Families make it all worthwhile, too. I remember well the guilty feeling that I was not spending sufficient time with my children, and the worry that they would think the babysitter was their mother. But even when we were working at home or going to a scientific meeting, our children were there and engaged and very much a part of whatever was going on or being done. How many PowerPoint presentations did I give, the background color or pattern for which was chosen by one of my children? How many times did one of my children stand on a chair and applaud and cheer at a platform session when everyone else applauded at the end of a stranger’s 10-minute talk? I have lost count! But our work was their work and their homework was our work and we all did it in the same room sharing pieces of everything with one another. Quality time? It is what you create out of whatever you do.

Take-home Lessons

If I step back and view my career born of unusual juxtapositions and my life at the interface from afar, it seems there are three overarching “take-home lessons” to be learned. I list them below not as advice, but rather, as a kind of “warm hand-off”, as is done between successive caregivers during the hospital stay of an inpatient. Use them as you will to create whatever you hope the future will be.

1. Science and Art are two sides of the very same extraordinarily beautiful coin. Do not be afraid to juxtapose them. Embrace their synergy. The world will be richer for it.
2. Structure and function are inexorably linked. Unlock one, and you hold the keys to the other. Fix one, and you will fix the other. Master them both, and you may prevent and cure human disease.
3. Legacy is everything. Honor what is good in the past; fuel what is promising in the future; and you will bring meaning and substance to the present.

Acknowledgments

This essay was written in gratitude to those who populate my professional and personal family trees.

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Fig. 1.
Max (left) and Samuel (right) Smul in Sadagora, Bukovina.

A **B** **Fig. 2.**

Palindromic sequences at which the restriction enzymes from *Hemophilus aegyptius*, Hae II (A) and Hae III (B) cleave double-stranded DNA.^{6,18} Cleavage sites on complementary strands are indicated by blue arrows.

Fig. 3.

Cartoon depicting the three-dimensional structure of hen egg white lysozyme (blue) and its substrate (red).⁹ The yellow arrow shows the cleavage that occurs at the active site of the enzyme. The turquoise box encloses the N-terminal 10% of the protein, removal of which from the denatured protein prevents its assumption of its native configuration and obviates enzymatic activity upon attempts at renaturation.