Gene–environment interactions

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During World War II, my father enlisted in the Army Medical Corps and trained as a medic. He was severely wounded during the Battle of the Bulge and received a Purple Heart and Bronze and Silver Stars: *great genes*. Decades later, I learned you could not have an MRI with two 30-mm machine gun slugs near your spine: *intrusive environment*. His and my mother's focus became education for their kids. Stimulated by the Alan Shepard (1961) and John Glenn (1962) space launches, I began designing and constructing rockets, launched in my back yard. I gave my father a list of chemicals to buy at Fisher Scientific, headquartered in Pittsburgh, Pennsylvania, where we lived. Eventually, my friends and I launched a small animal a few hundred feet up and parachuted it back alive. Our feats were figuratively recapitulated in the book *Rocket Boys*[1] and the movie *October Skies*.[2]

I was the first in my extended family to attend university, matriculating at the University of Delaware to study chemistry. My adviser, Don Dennis, a biochemist, maneuvered me into that field. For graduate school, he steered me to his mentor at Brandeis. After my interview there, taking the subway back to the airport, I stopped in Cambridge. With little to lose and a touch of chutzpah, I walked unannounced into the office of John Edsall, the renowned protein chemist at the Harvard Biological Laboratories. He told me to apply. I was accepted but soon learned I was classified as 1-A for the military draft at the height of the Vietnam conflict. Don Dennis called the chair of the Harvard admissions committee, who suggested that I shift my admission to the biochemistry department at the medical school, perhaps improving the chances of an educational deferment. Who were we to argue with the 1962 Nobel Laureate, Jim Watson? I flunked my draft physical because of a knee injury and started graduate school. My father was delighted I did not go to war.

REPEATED SEQUENCES

I chose as my dissertation advisor Charles Thomas, who was studying double-stranded DNA phage genomes, in part based on the work of a recent student, Thom Kelly. (Kelly subsequently trained with Ham Smith at Hopkins; their work documenting the first recognition sequence for a restriction enzyme won Ham a Nobel Prize.) Our lab was the first to restrict eukaryotic DNA; the smear on the gel, while pioneering, was not particularly enlightening. When H.G. Callan, who imaged lampbrush chromosomes in *Xenopus*, came to the lab for a sabbatical, I learned cytology and electron microscopy and was encouraged to explore the frequency and organization of repetitious sequences, including the recently described "satellite DNA" of eukaryotes.[3,4] Since our lab was in the medical school, I began recognizing potential human applications of DNA technologies. Along with friends in Science for the People, I protested the nascent observational study of children with 47,XYY syndrome, because of both its sociopolitical motivations and its unsound protocol.[5] It was discontinued, and I was emboldened and stimulated to study ethics, an activity that has persisted to the present. Charlie arranged for us to observe one of the early amniocenteses performed for a genetic indication at the Boston Lying-In Hospital. That day I decided to attend medical school.

MEDICAL SCHOOL

I enrolled in Harvard Medical School, where students selected their own faculty adviser. I approached Lew Holmes at the Massachusetts General Hospital, who was most supportive. On my medical genetics elective, he sent me each morning to the pediatric wards to review each new admission and report cases that might have a genetic contribution. Of course, many did, and we would slip by, usually uninvited, to see what the medical genetics team could learn. I learned that even in the best institutions, genetics was usually an afterthought and contributed little to clinical revenue. Another mentor was Hugo Moser, then superintendent of the Fernald School in Waltham. We reconnected a decade later at Johns Hopkins and enjoyed several fruitful collaborations. In my last term at Harvard, I became one of the first two students funded by the Medical Scientist Training Program grant just awarded. My younger brother was also on the road to medical school: genes again?

INTERNAL MEDICINE

When it came time to choose a medical specialty, knowing that I wanted to be a medical geneticist and stay in Boston (where a girl I had met in first grade married me and supported my medical education), I applied to both medicine and pediatric residencies. The match directed me to the Peter Bent Brigham Hospital, where I trained in medicine. During internship,

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Victor McKusick was our visiting professor. I had already secured a medical genetics fellowship with Arno Motulsky, but Eugene Braunwald, my chief of medicine, told me in no uncertain terms to meet with Victor, who was the Osler Professor at Hopkins and the chair of the Department of Medicine.[6] After an hour I was smitten and signed on to be his fellow. When I arrived in Baltimore on 1 July 1977, still in my Brigham scrubs after an early-morning flight, I learned that Victor didn't run a lab; he didn't have a fellowship opening for me; I would be a senior resident on the Osler Medical Service; and he was about to see a family with Marfan syndrome (MFS) in his private office and would I please join him.

MARFAN SYNDROME

My prior experience with MFS was limited. I had admitted a young pregnant woman with an aortic dissection; neither she nor the fetus survived. Victor's two-generation family was interested in whether the children of the proband, who had miraculously survived a type A dissection, were affected. This one encounter had more to do with my career than any other. (Ironically, after many years the family turned out to have familial aortopathy, not MFS.) I was immediately enmeshed in MFS, a disorder in need of clinical, basic, and translational research. Under the mentorship of Victor and Tony Murphy, I wrote a successful RO1 application to study β-blockade.[7] I also wrote two postdoctoral fellowship applications; when both were awarded, Victor appointed me a junior faculty member, meaning that "technically" I never did a fellowship.

Over 15 years, I published studies of MFS with colleagues at Hopkins and elsewhere who represented 18 distinct specialties of medical and biologic science. On this path of collaboration, many academic medical geneticists will find success. A pediatric cardiology fellow, looking for a one-month research experience, was referred to me for a project. Hal Dietz was gullible enough to agree to identify the MFS basic defect, something that had eluded us for years. We focused on one of Bryan Hall's Kentucky families. With some added time, working with Clair Francomano and Garry Cutting, he refined the linkage to 15q.[8] In short order, he found the basic defect in *FBN1* in two sporadic patients I had followed for many years.[9]

In 1978 I called together several of my patients and their families to discuss formation of a support group. Victor hosted this meeting in his home. Several participants were both affected and health-care professionals, and they became the drivers of the nascent organization. The National Marfan Foundation (now the Marfan Foundation; http://www.marfan.org) has thrived in its original tripartite mission: research, family support, and public awareness. Over the 30-odd years that I have been involved in MFS research, life expectancy has increased by about 30 years.

DESERT STORM

The hiatus after Vietnam was salutary for military academic medicine. I enlisted, became the Army's medical genetics consultant to the Western Hemisphere, lectured at its medical school, saw patients at Walter Reed Army Medical Center, and rounded on the wards, where the residents called you "Sir." In 1991 we invaded Kuwait and folks like me were immediately ordered to head battalion aid stations at the front line. Sane heads prevailed for me and I continued to go daily to a station where more Americans were shot every day than in the desert—the District of Columbia. I "retired" as a lieutenant colonel and felt I gave some payback to my legacy.

AMERICAN COLLEGE OF MEDICAL GENETICS AND GENOMICS AND PRINCIPLES AND PRACTICE OF MEDICAL GENETICS

I was privileged to serve on the ad hoc committee formed by the American Society of Human Genetics in 1990, during Mike Kaback's presidency, to initiate a professional college dedicated to "clinical genetics." David Rimoin chaired this group, and the American College of Medical Genetics and Genomics became a legal entity.[10] From David, who served as the founding president for 6 years, I learned how to organize meetings and get an agenda accomplished with little administrative support, which were essential skills when I became the second president.[11] I chaired the publication committee that recommended that we initiate our own journal and even coined its name, *Genetics in Medicine*.[12] David also enlisted me as a coeditor of *Principles and Practice of Medical Genetics*, and together with Mike Connor and Bruce Korf we produced four editions.[13] We begin work on the seventh edition later this year.

CONCLUSIONS

I recently became the chair of the University Faculty Senate of the University of Pennsylvania. The year is full of promise and considerable challenge. The first challenge was to address the 6,500 graduates and their 20,000 guests in Franklin Field—the most anxiety-provoking 4-minute speech of my career. I concluded with, "Don't be afraid to change your plan, *but only if you have one*." This is advice I have always provided any mentee.

I have couched this Legacy article in terms of how I arrived rather than what I have accomplished. The present remains exciting and stimulating, keeping me active for the near term. After that, I'm working on a plan. Finally, as my daughters will attest, rooting for Pittsburgh sports teams is clearly an autosomal-dominant trait; it should be listed in OMIM.

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DISCLOSURE

The author declares no conflict of interest.

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