

Bruce A. Beutler

Biographical



One of the happiest days of my life

It was 2:30 a.m. on October 3, 2011, and I was at home, in my small condominium in San Diego, CA. I was sleepless, having recently returned from a trip to Hong Kong. There I had shared the Shaw Prize in Life Sciences: one of a series of prizes in recent years. The previous afternoon, as we visited our mother in La Jolla, my brother Earl had remarked that the Nobel Prize in Physiology or Medicine would be announced the next day. He also had asked if I was going to win it this year. This was on my mind as I lay awake.

Bleary-eyed, I looked at my cell phone to see if there was any email. There was a message: just one. The title line seemed to be “Nobel Prize.” I reached for my glasses, looked again, and found I was correct. Nobel Prize. Perhaps this year the Committee had made a mass e-mailing of the announcement to members of various National Academies? I opened the message and read the first lines of a letter from Göran Hansson ...

“Dear Dr Beutler,

I have good news for you. The Nobel Assembly has today decided to

award you the Nobel Prize in Physiology or Medicine for 2011. You will share the Prize with Drs Jules Hoffmann and Ralph Steinman. Congratulations!’’

I was too excited to read more at that moment, and hurried downstairs. I called Betsy Layton, my longtime colleague and Administrative Manager. She was in Dallas, preparing the way for our relocation from the Scripps Research Institute to UT Southwestern, where we had earlier done some of our most important work. She had worked with me over the past 25 years, and had played an important part in finding the Lps mutation for which the Prize was awarded. I woke her from a sound sleep. “Bets,” I said tentatively, “I think I won the Nobel Prize!” She was ecstatic, but I cautioned her that I had to confirm it, and kept her on the line.

I tried to access the website Nobelprize.org, but found I couldn’t; there was too much traffic. Then I went to news.google.com. I searched for my name, and within a minute or two, began to see it in reports emanating from all over the world. It was true. I told Betsy so, and she was so happy she began to cry! Yet still I was somehow disbelieving and only over the days and weeks that followed did the new reality settle in my mind.

Nadia Krochin, my dear friend and companion of many years, called me from the east coast before I could call her, and left a message on my voice mail that was almost incoherent with joy! I called my brother Earl; then my brother Steve; then my sons; then my friend Ari Theofilopoulos. I waited until about 4 a.m. to call my mother. Each person, though awakened abruptly, was nearly as happy as I had been.

By this time, my cell phone was ringing almost constantly, and it didn’t stop ringing until late afternoon. Mostly reporters were calling, and I attempted to respond immediately to a few of them, hearing a constant beeping of incoming calls in the background as I did. Among those to whom I spoke during those first hours was a

National Public Radio anchor, and it was on NPR, driving to work in various parts of the country, that many of my friends soon heard the news, along with my initial reaction. Emails were arriving every few seconds, and by the end of the day, I had more than a thousand of them. I realized it was hopeless to reply to them, and instead, via Betsy, I advanced my pre-existing plans to fly to Dallas. While waiting for my 10 a.m. flight, I went for a haircut earlier scheduled for 8 a.m. Hannah Andrusky, a charming lady who had cut my hair each month for several years, agreed to meet me an hour early that morning. I was her first client of the day, and she, too, knew of the Prize. She was as delighted and proud of me as everyone else had been. The haircut was free.

In Dallas I was greeted as a hero. A press conference was arranged for the next day, and after introductory speeches by the Dean, President, and Past President of UT Southwestern Medical Center, I stepped to the podium, met by a warm standing ovation. I spoke for several minutes from the heart, without slides, notes, or preparation of any kind. I felt a sense of self-confidence I hadn't known before. After all, I was a Nobel Laureate. Everyone present was elated and wished me well. I talked a bit about my life, about the steps that had brought me to the Nobel Prize, and also about some of the struggles and strains this entailed.

My background

All of my grandparents immigrated to the United States to escape persecution as Jews, and I was reminded of this often from an early age. World War II had ended only 12 years before I was born, and recollections were fresh. My father was born in Germany, my mother in America to immigrant parents. My siblings, my cousins and I were always strongly conscious of our European origins, and of the extreme anti-Semitism that had recently prevailed in Europe. Probably we all felt a need to excel partly because of these facts; to show that we were as good as the other children in our schools.

My mother's parents, Aral ("Harry") Fleisher (1895–1953), and Miriam ("Mary") Fleisher, née Krasne (1893–1966), were both from Kiev, and moved separately to the USA near the turn of the century, settling in Chicago where they met and married in 1922. Harry initially worked in the insurance business. However, he was persuaded to join the company of Mary's father, Louis Krasne (L. Krasne and Sons). Mary and her brother Isador traveled to the west, ultimately settling in Tulsa, Oklahoma where they established a branch of L. Krasne and Sons that traded in "Leather and Findings." My mother, Brondelle May Fleisher, was born in Chicago but raised in Tulsa from the age of 11. She was the second of three children (Beverly was older and Lois younger), and she survives both her sisters today.

My mother's father died before I was born, but I knew my maternal grandmother well. Afflicted with a brittle form of diabetes (oddly at a mature age), she lived with us, was known as "Bubbie," and took care of me during my first few years of life. I remember her as a warm and kindly old woman with a strong Yiddish accent and extremely long hair, nearly touching the ground. Almost blind, she would spend much of her time in the garden, pulling weeds from the lawn, or otherwise trying to be useful. She was happy to talk to me, or walk with me or explore the yard. One of our routines was to "search for the Fountain of Youth" (which always turned out to be a drinking fountain in the back yard). She died within days of having a myocardial infarction at our California home in 1966.

My father's parents, Alfred Beutler (1891–1962) and Kaethe Beutler née Italiener (1896–1999) were both physicians: he an internist with a particular interest in cardiology, and she a pediatrician. They emigrated from Berlin, Germany in 1935 to escape Nazi persecution. I knew my father's father only slightly as he lived in Milwaukee, WI, visited only occasionally, and died when I was only four years old. My grandmother Kaethe, on the other hand, lived to be 102, residing near my parents' house for many of the last 40 years of her life. I had innumerable interesting conversations with her, beginning at a young age and continuing into my 40s. She was,

on the one hand, kind to all her grandchildren, generally patient, and attentive to us. But occasionally she would lose her temper and shout at us with a strong German accent, which could be quite intimidating. She had an extraordinary vocabulary in English, was highly informed of current events, especially national and local politics, and spent much of her time reading books and political magazines. She was a lover of classical music and a competent pianist, who in her 60s and 70s, gave lessons to children in her neighborhood. She remained intellectually sharp, trading on the stock market and even learning to program a computer in her late 80s and early 90s. She had high standards, was quite strict about punctuality (once excoriating my sister when she showed up to an appointment at 3:17 pm rather than the designated 3:15 pm), and was hard to impress. She was not one to “ooh” and “ahh” over a child’s drawing or any other minor accomplishment. On the other hand, she did encourage all of us, often through unstinting praise of great achievements in the world at large. It may well have been from her that I first heard the phrase “Nobel Prize” when I was still a small child, and on rare occasions, when I talked to her about science, I recall her saying “maybe someday you will win the Nobel Prize.”

My grandmother was never comfortable as a Jew in German society at any time she lived there, although she was the physician to children of prominent gentile families in Berlin. Among her patients was the son of Magda Goebbels (from her marriage to Günther Quandt), about whom she spoke to me a few times. She described Magda as an “elegant, beautiful woman” who was quite pleasant prior to her marriage to Josef Goebbels, whereafter she visited no more. My grandmother did not foresee the Holocaust, even two years after Hitler’s rise to power, but did foresee that her three children (my father, Ernst, his older brother Frederick, and his younger sister Ruth) would be denied an education and would have no future in Germany. She was the prime mover in the family’s decision to leave. For a time, it was undecided whether they should emigrate to Palestine or to the United States. My grandfather actually visited Palestine, but found opportunities for physicians to be limited, and decided in favor of moving to America. This was reportedly contrary to my grandmother’s

wishes. “He asked me where I thought we should go. I said ‘Palestine,’ so of course we moved to America,” she sometimes recounted. In the years that followed, she regretted that she could not take part in building the modern state of Israel. At the same time, she was relieved that her children did not need to fight in the wars that beset Israel from its founding.

Both of my parents were born in 1928, my father in Berlin, Germany, and my mother in Chicago, IL, USA. My father was said to have been a somewhat difficult child, often in conflict with his mother. However, he performed extraordinarily well at school, and at the age of 15 was enrolled in a special program developed by Robert Maynard Hutchins, then President of the University of Chicago, which permitted him to finish high school and college within two years and then go on to medical school. This he did, graduating as the valedictorian of his class, with a doctorate in medicine at the age of 21. He specialized in hematology, and in time became the pre-eminent academic hematologist of the 20th century. His scientific contributions extended to many areas of biomedical science, and he received numerous awards and distinctions in recognition of his work, including the Gairdner Prize in 1975, and election to the National Academy of Sciences and the Institute of Medicine in 1976. His most celebrated achievement was the 1962 discovery of random X chromosome inactivation in humans, made independently of Mary Lyon, who discovered it in mice. He made many other advances as well, in diverse fields of study, and he was to influence my own career dramatically.

My parents met at the University of Chicago, when my father was in his junior year of medical school. My mother was an undergraduate there, majoring in mathematics. They married June 15, 1950, and remained together until my father’s death in October of 2008. In addition to me, they had three other children: Steven in 1952; Earl in 1954; and Deborah in 1962 (Figure 1). Like me, Steve and Debbie became physicians; Earl became a successful businessman. Our early years were mostly spent in southern California, because my father moved there in 1959 to accept a position as Chairman

of the Department of Medicine at the City of Hope Medical Center in Duarte. My mother worked as a homemaker for about 18 years, spanning most of my childhood. She then began a late career as a technical writer, retiring in her mid-60s.



Figure 1. My early life and family. Clockwise from top left: My parents, standing in the front yard of our house in Arcadia, early 1960s (backdrop: a lantana bush often covered with skipper butterflies). Photograph taken of me at about 2 years of age, either before or after departure from Chicago for California. My maternal grandmother, Mary Fleisher (“Bubbie” to my sibs and me). My brothers and infant sister posing in front of the living room fireplace in 1962. From left: Steve, Bruce, Debbie, and Earl. My brothers and me, in the front yard of our home, ca. 1960. From left: Steve, Earl, and Bruce.

CA childhood and friends

I was born in Chicago, IL, on December 29, 1957. But I have only fleeting memories

of my first years there. My earliest memory is of newly fallen snow in the autumn of 1959. Seeing that the world outside had changed overnight, I asked “Who did that?” I also remember crying when movers came to take everything out of my room, as the family was relocating to California, where, from the age of two, I grew up in Arcadia, a northeastern suburb of Los Angeles. I have warm recollections of my childhood in California, and often have dreams in the setting of the adobe brick house where I grew up, with its orange terra cotta tile roof, one-acre yard, orchard crammed with fruit trees, guest house (which served as my room from the ages of 12–16), large front lawn (which we called “the field,”) and swimming pool (Figure 2). Generally speaking, I recall sunshine year round; heavy smog and hot weather during summer months; snow on the surrounding peaks and frost on the lawn in the mornings during winter; family vacations to national parks; and the fact that I had a strong interest in nature (particularly in animals). Over the years, I raised many animals (dogs, ducks, rabbits, mice, chameleons, tropical fish, turtles, and zebra finches), watching them and generally marveling at their behavior. As I grew up, I did lots of hiking (chiefly in the San Gabriel Mountains), birding, and bicycling. There were stresses to be sure: quarrels with my sibs and worries about deadlines in school, but nothing serious. On the whole I was very happy, even if I didn’t always realize it.



Figure 2. The house where I grew up (Arcadia, CA, early 1960s). A. Partial view of the front yard from the front gate, showing banana tree (bottom left) rose bushes and rose trees, a young sycamore tree and eucalyptus tree, olive tree, and adobe brick house with terra cotta tile roof. B. Partial view of the back yard and swimming pool, taken from inside the “guest house” (ultimately an annex to my room).

I began first grade early (at age 5), attending public school until I was 13 years old. I was then admitted to Polytechnic School, a college preparatory school in Pasadena, CA. The content of the curriculum at Polytechnic, and the pace at which we were taught, was quite different from what I had experienced in public school. It was something of a renaissance for me, and I regretted having wasted so much time beforehand. Not only was I taught more, and taught better at Polytechnic than at public school, but I also had exceptionally smart friends, and have remained close to some of them to this day. David Brittan, Paul Spiegel, Bob Kleinberg, John Taylor, and David Horowitz were among those friends, and with them, I could discuss almost any topic of the day, as they had a wide range of interests, spanning music, politics, literature, and science.

During three years at Polytechnic, I learned a lot about many things, and certainly changed a great deal, with some mental transformations literally occurring from one day to the next. For example, when I was 15 years old, I attended a performance of Bach's St. Matthew Passion. My father had intended to go, but could not, as he needed to rescue my brother Earl, who had been bicycling from San Francisco to Arcadia, and had become exhausted on the way; hence I went in his place. I had been exposed to classical music in my home as a child, but it didn't make any special impression on me. Yet I was completely electrified by this live performance of Bach's great choral masterpiece, the first I had heard, and at once began listening to other choral music and collecting it on vinyl records, especially pieces by Bach, Handel, Vivaldi, Mozart, and Haydn. I remember arranging my curriculum in such a way that I could bicycle to school early in the morning (a distance of eight miles), complete my classes by late morning, and then bicycle home to listen to a radio concert of Renaissance music in my father's study. Later I would do my homework (generally until quite late at night, and usually accompanied by Bach). I have remained a music lover ever since, ultimately settling on Bach as the center of my musical world. But although music became a deep and enduring interest of mine, I never learned to play any musical instrument proficiently.

Early interest in science

From childhood, living things appealed to me aesthetically. I could relate to them, and I was amazed by their similarity to humans. I was aware that life forms had changed continuously on earth over many millions of years, and concepts of genetic variation, natural selection, and inheritance were second nature to me, even from the time I was in elementary school.

In hiking and birding, and in looking at microbes through a microscope (one of my favorite diversions at some point), I enjoyed the observational side of science, which is where scientific inquiry normally begins. It was during high school, in the rich intellectual environment I have briefly described, that I first began to wonder about unanswered questions in science. The ability of inanimate molecules to assemble themselves into living matter was something that I found immeasurably interesting. My oldest brother, Steve, once introduced me to a quotation he attributed to [Camus](#): “Life is the disease of matter.” Probably it was actually from Goethe, who as I later learned, wrote “Viewed from the summit of reason, all life looks like a malignant disease.” The idea resonated with me, not in a morbid sense, but because life was a process that compelled matter to do its bidding, co-opting it more or less automatically, and endowing it with special properties not seen in the inanimate world. In the early 1970s, I read the second edition of [James Watson](#)’s “Molecular Biology of the Gene” (also a gift from my brother Steve, then in college at the University of California at San Diego) from cover to cover, and understood for the first time how DNA specifies the synthesis of proteins with specific functions, which in turn permit DNA replication, the development of a complex organism, meiosis, and the propagation of species. I became even more eager to participate in the study of living things, and to be an experimentalist rather than merely an admiring witness.

In high school and in college, I began to work in my father’s laboratory, and it was at this stage that I began to do authentic research. I was guided by my father and his interests, and learned to assay erythrocyte enzymes, and to characterize their

electrophoretic mobility. One of the enzymes I studied most was glutathione peroxidase, unusual because it was a seleno-enzyme. At one point, striking out on my own a bit, I decided to see whether bacteria might have glutathione peroxidase, and whether it might be subject to biosynthetic control based on the availability of selenium, like the genes of operons, which had been described not too long before by [Jacob](#) and [Monod](#). Lysing *E. coli*, I first found that there was no glutathione peroxidase activity. My father suggested I should add sodium selenite to the culture. I did so, and found considerable activity, which I interpreted as a success: I believed the selenite had induced synthesis of the enzyme. “Boil it,” said my father. The activity remained and was even slightly increased. Moreover, inorganic sodium selenite (and even more so, seleno-cysteine) exhibited catalytic activity. When seleno-cysteine was incorporated into the protein, this activity was enhanced many thousand fold. We proposed a reaction mechanism based on the catalytic properties of selenium in distinct oxidation states. We also found a polymorphism of erythrocyte glutathione peroxidase activity in members of my own family, and an electrophoretic polymorphism in others. I began to think as a biochemist, and to some extent, also as a geneticist, but only in a rather elementary way at that stage.

My father as a role model

The foregoing vignette tells something of how my father influenced me. I was thrilled when he received the Gairdner Award, and when he was elected to the National Academy of Sciences, both of which occurred during my teenage years. Indeed, I sought to emulate him and took his advice seriously. When he suggested I read “Arrowsmith” by [Sinclair Lewis](#), and “The Microbe Hunters” by Paul de Kruif, I did so, and just as they had earlier affected him, they also affected me. Among the most important pieces of advice he gave me was to go to medical school. The explanation he gave was that disease often reveals new and important biological principles; also, as a physician in training, one acquires broad knowledge of anatomy, physiology, histology, pathology, and pharmacology: sciences that come into play in understanding many biological phenomena. Throughout his life, my father was an

advocate of working on “something important,” rather than what he saw as esoteric topics. Generally speaking, he preferred authentic clinical research (with patients) to research with mice, and research with mice to research with flies or other distant model organisms. Notwithstanding his strong genetic and evolutionary orientation (which we shared), he tended more toward applied research than I myself did. And his judgment as to what was important rested chiefly on his medical experience, which was quite extensive.

With a strong focus and a sense of mission, I completed high school early (at the age of 16) and enrolled at the University of California at San Diego (UCSD), in Revelle College. I had taken certain examinations that gave me “advanced placement” credit, and I pursued an ambitious schedule in college. I worked through two summers, and graduated at the age of 18. I was a good student, but not an outstanding one. As a teenager and even for some years beyond, I was a bit emotionally volatile, often distracted by love interests, and generally speaking, in too much of a hurry. I took on an enormous course load, wishing to get through college quickly, go on to medical school, and become a scientist. It was an exciting time in biology, after all, with extraordinary advances in molecular cloning beginning to dawn. I was aware of what was going on, and impatient to be part of it. To my friend high school friend David Brittan (also my roommate for a time in college), I remember saying with frustration “The train of science is leaving without me.”

But despite the hurry, I did learn a lot, and only realized how much later on. I had a truly stellar introduction to genetics in the laboratory of Dan Lindsley (Figure 3a), a distinguished *Drosophila* geneticist interested in spermatogenesis and spermiogenesis in the fly, among other topics. In his lab, I attempted to map the gene for hexosaminidase (a project inspired by my father, who had studied this enzyme in humans, where hexosaminidase deficiency causes Tay-Sachs disease). When I was 18, I spent the summer working in the lab of Abraham Braude, most immediately with his postdoctoral fellow Arthur Friedlander (who later became well known for his studies

of anthrax lethal factor). In Braude's lab, I first heard the word "endotoxin," also known as lipopolysaccharide, or LPS. I understood it was pyrogenic, capable of activating leukocytes, and also heat stable (which made it a particular problem in our studies of chemotaxis). All glassware had to be heated to 180°C to destroy contaminating LPS. I also knew that Braude had tried to passively immunize humans against LPS to protect them against Gram-negative septic shock. But my interest in LPS was casual and tangential at that stage, probably because its biomedical importance was still an abstraction to me. I had never seen a patient with sepsis, and didn't grasp what a serious clinical problem it might be. The question of an LPS receptor did not occur to me at that time. I did not remotely imagine that searching for it would form the core of my Nobel Prize-winning work two decades later.

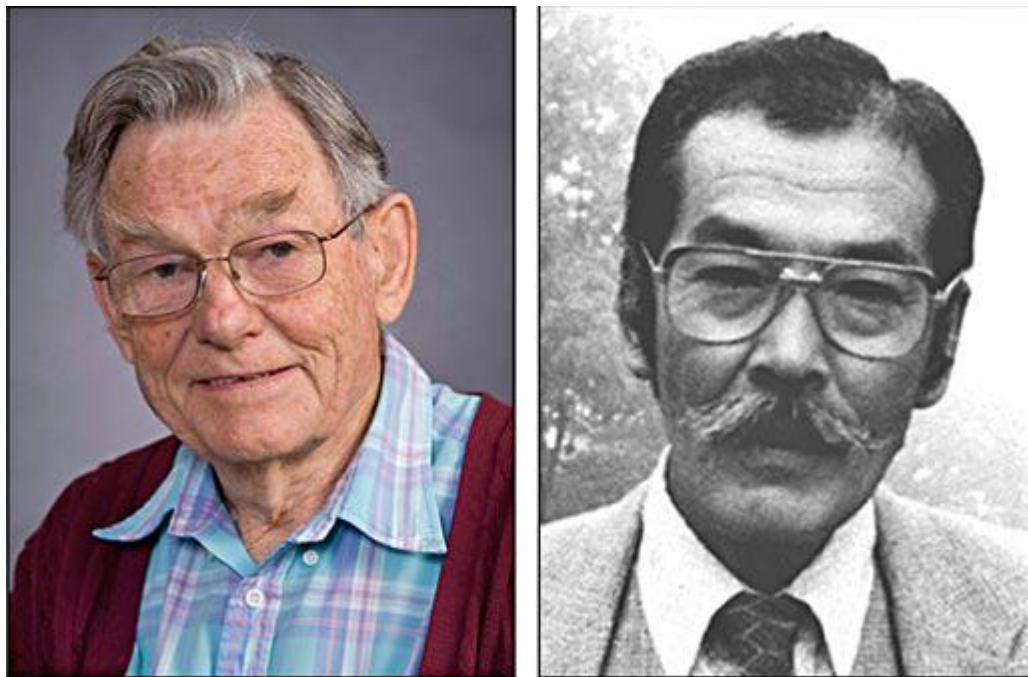


Figure 3. Teachers who influenced me. Left: Daniel Lindsley, photographed in the early 1990s. Right: Susumu Ohno (from a biographical memoir by Ernest Beutler, National Academy of Sciences, USA).

After completing college, I had still more exposure to genetics in the lab of Susumu Ohno (Figure 3b), a friend and colleague of my father at City of Hope Medical Center. I worked with Ohno for about nine months, and spent still another summer with him during medical school. A famous mammalian geneticist, Ohno had demonstrated that

the Barr body observed in cells of female mammals was a condensed X chromosome. He had also developed the thesis that evolution depends upon gene duplication. He had written extensively on the phylogeny and origin of sex chromosomes. And he had observed that the genetic content of the X chromosome tends to be strongly conserved in all mammalian species. In short, he was a remarkable theoretical biologist at a time when experimental tools were not nearly what they are today.

Ohno inclined toward immunology after spending a sabbatical at the Basel Institute for Immunology. He hypothesized that major histocompatibility antigens act to anchor organogenesis-directing proteins. He adduced considerable experimental evidence supporting this hypothesis ... which we know today was entirely incorrect! The time I spent in Ohno's lab, working on this very subject, was quite enlightening for me from many points of view. In hindsight, perhaps the most important – if brutal – lesson was that even extremely intelligent scientists can deceive themselves if they embrace hypotheses too passionately. But I also learned much about immunology as it was understood in the mid-1970s.

I applied to several medical schools, confident that I would be admitted to most of them. I had good grades, extensive experience in laboratory research, several publications (including one first-author paper in *Cell*), and MCAT scores in the top percentile. But in the end, I was admitted to only one medical school: the University of Chicago. All others declined my application, perhaps because I was so young, and perhaps because I was unreservedly interested in science rather than clinical medicine. So I must be grateful to the University of Chicago for the chance it gave me. Luckily, it was (and remains) an outstanding institution. In the fall of 1977, I moved to Chicago and began my studies there at the age of 19, the youngest member of a class with more than 100 students.

Medical school

My first impression of Chicago was that it was a “real” city compared to the southern

California suburbs I had known. But it was also somewhat dangerous (where I lived, at least), and comparatively unwelcoming. The Chicago winter was something for which I was not prepared. I arrived dressed as a Californian, and nearly froze when I tried to walk the mile from the University to my apartment during the first winter storm, in high winds and sub-zero temperatures. As I remember, my ears were insensate for about an hour, and I initially feared they would become gangrenous and fall off! I recall the first years as quite challenging. Anatomy and neuroanatomy were especially tough, requiring spatial memorization of a type that was unfamiliar to me, but in the end, both classes were rewarding. My classmates were for the most part smart and competitive, and I had to struggle to do well. I particularly enjoyed histology, physiology, and microbiology classes.

When it came to my introduction to clinical medicine, the work was more demanding than any I had ever known. Ultimately this was beneficial, because I came to expect equivalent discipline of myself and others when I worked in the laboratory. But I did not get the same joy out of clinical work that I did from laboratory work. I was often uncertain as to whether particular therapies and practices had a sound rational basis, and when patients got better, I did not always feel I could claim credit for it. After all, there was no control group. And very rightly, there was no leeway for experimentation on the wards. I did manage to work for some months in the laboratories of Patricia Spear, an outstanding young herpes virologist, and Barry Arnason, a neurologist with a strong interest in multiple sclerosis. But overall, there was little time for research, and I began to miss the lab.

In 1980, when I was 22, I married Barbara (Barbie) Lanzl, then a dental student at nearby University of Illinois. She was three years older than I, and had previously been married to my friend and medical school classmate Jiri Sonek. The marriage lasted 8 years, with phases in Chicago, Dallas, New York, and Dallas again, before ending in divorce. We had three bright, healthy sons, two born in Dallas and one in New York.

Internship and residency

I graduated from the University of Chicago in 1981, and again acting according to my father's advice, decided to spend at least a year or two in residency, learning more about clinical medicine. I was matched with the internal medicine internship program and the neurology residency program at UT Southwestern Medical Center in Dallas. Dallas was my top choice, and arguably offered the finest clinical training in the country. It was known for giving interns and residents considerable responsibility and autonomy. During the year of my internship, for example, two interns and one resident would run the internal medicine emergency room alone through the night, with no attending physician present. And when necessary, medicine interns were expected to perform fairly invasive procedures, including intubation, placement of subclavian lines, cardiocentesis, insertion of chest tubes: in short, whatever was required, particularly during emergencies (which were not uncommon).

My father's twofold rationale in suggesting an internship and residency rather than a laboratory fellowship had been that I would become "a finished doctor;" also that I would have something to fall back on in the event that research did not pan out for me.

As to the first point, I believe he was correct. At least the year I spent in internal medicine internship taught me many things I hadn't known as a senior medical student. By the time I had finished, I feared no medical emergency; I felt secure in doing whatever needed to be done. But I also knew that medicine was not for me. I badly missed research and longed to return to it. I felt obligated to finish at least one year of neurology residency and did so. I learned quite a bit about neurology, which sometimes helps me to the present day in assessing mutations in mice. But perhaps the residency year gave me a bit more clinical training than I ever wanted.

As to the second point, my father was certainly being prudent. But to my recollection, I was supremely confident of success in science. I felt that no matter which lab I

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