FROM BOSTON TO NEW HAVEN: A JOURNEY OF DISCOVERY

Irwin M. Braverman

I want to thank Kai Erikson for the opportunity to participate in the Intellectual Trajectory series. It isn't often that one has a chance to reflect on the events of one's life and then be able not only to write it down for publication, but also to have a captive listening audience.

I begin with my family origins as many of my predecessors have. My two grandfathers came to the United States from Russia just before World War I to make their fortunes and then return to their families. However, the war intervened and they were prevented from returning. The political situation in Russia subsequently became chaotic, and their families—recognizing their futures were problematic—uprooted themselves to join them in 1921. My mother's family left in a hurry—a twenty-four-hour decision—one week ahead of the Bolsheviks who were advancing on their town. My mother and father met and married in Chelsea, Massachusetts. My father was a skilled boot maker and went to work in a shoe factory. My mother went to work as a seamstress in a dress factory. Although neither of my parents went to college, they finished high school, were well read, and learned English very quickly. My father spoke Polish, Russian, and Yiddish as well as Esperanto, which he was taught in school. I was born in 1929, and when I was four we moved from Chelsea to Dorchester, a Boston suburb. Two years later, my father was able to open a small store, similar to a Wawa today, in the Lower Mills area of Dorchester, where I attended the Gilbert Stuart School in the first and second grades. We were the only Jewish family in that part of Dorchester. After two years of being made unwelcome, we moved one-quarter mile away to Mattapan, a predominantly Jewish suburb. My brother Jordan, seven years younger, arrived at this point to complete our family. My father continued to have a reasonably profitable store until early in World War II when the anti-Semitic ravings on radio by Father Coughlin from Detroit produced a boycott that destroyed his business. I finished out my elementary school education at the Charles H. Taylor School, named

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Irwin M. Braverman, Professor Emeritus of Dermatology, was a member of the School of Medicine faculty from 1962 to 2010. After studies at Harvard College and Yale School of Medicine, he served as intern and resident in Internal Medicine and Dermatology at Yale-New Haven Hospital; in 1973 he was promoted to professor of dermatology. Braverman won the Blake Teaching Award for Most Outstanding Teacher in Medical Sciences in 1977 and the Distinguished Alumni Service Award from the Association of Yale Alumni in Medicine in 2011. He was previously vice chairman of the Department of Dermatology and a member of the medical school's Committee on Admissions and its Appointment and Promotions Committee. Braverman's research publications are focused on the cutaneous microcirculation, pathogenesis, and therapy of cutaneous T-cell lymphoma, and chronological and sun-induced skin aging. He is the author of *Skin Signs of Systemic Disease* (1970, 1980, 1998), which was published in Spanish (1973) and Taiwanese (1982) editions.

after one of the family members who owned the *Boston Globe* and whose son Charles H. Taylor, Jr., was provost at Yale during the presidency of Kingman Brewster, Jr. Were there prophetic messages here (Gilbert Stuart and Charles H. Taylor)? By the sixth grade, the Boston school system had thoroughly infused me with the Pilgrim narrative and the colonial history of Boston and New England, and by the ninth grade, with the meaning and obligations of American citizenship. These elements became part of my narrative as a first-generation American.

I attended the Boston Latin School, a public school founded in 1635, one year before Harvard College. This school—admission to which was based on grades and/or examination—has served as the preparatory school for Boston students. It was all male, regimented, and demanding. There were daily homework assignments of four to six hours a night. Twelve hundred students entered in the seventh or ninth grade, but only two hundred graduated. The school instilled study habits that taught one how to handle enormous amounts of classroom and homework material. Although Boston Latin has been described by former students as Parris Island for teenagers, the school has served as the escalator to opportunity and Ivy League colleges for working-class Irish, Jewish, and Italian boys since the beginning of the twentieth century. Today it serves the same purpose for Boston's Asian, black, and other minority students. Boston Latin School is located on Avenue Louis Pasteur. Immediately adjacent on the left are Harvard Medical School and its dormitories. On the other side is Simmons College. Around the corner on the Fenway are the Isabella Stewart Gardner Museum and, a short block away, the Boston Museum of Fine Arts. At least once a year my mother made reference to the Harvard Medical School and its potential place in my future.

The classical curriculum consisted of Latin and one or two of the following languages—Greek, French, Spanish, and German—along with physics, chemistry, math, history, and English. There was a major emphasis on the history of England from its earliest times to the American Revolution. I once could recite in chronological order the names of all the kings and queens of England. The curriculum had no formal classes in the arts or music. Rather there were after-school clubs for those interests, as well as other interests, supervised by a faculty member. A school orchestra gave concerts twice a year, and a drama club put on an annual full-scale production. The school had a gymnasium, but it was used only for military drill and by the school's basketball team. All Boston schools from ninth to twelfth grade participated in a junior ROTC. We wore uniforms, had officer ranks, and nonfunctioning World War I rifles that we used for close order drill and marching in the school yard. Athletics or exercise for non-team students was nonexistent. There was an annual school boy parade in downtown Boston each May which drew thousands of onlookers. Each high school fielded a drum and bugle corps in addition to their marchers. There was a formal panel of judges to give an award to the best-performing school.

Because we were the only high school in Boston that did not have art or music as part of the formal curriculum, several of us who were members of the art club were given free formal instruction, two afternoons a week for one year, in watercolor, charcoal, pastel, and pencil techniques and in drawing from sculpture and life at the art school associated with the Boston Museum of Fine Arts.

Today the school is coeducational, uses its gymnasium for athletics, and has art and music in the curriculum in addition to the classical studies. The rigor has been relaxed so that four hundred now graduate from the same 1,200 entering students. The school continues to act as a funnel for Boston students to college, especially Harvard.

In 1946 when I graduated, ordinarily one hundred students would have been accepted to Harvard, but only twelve were. World War II had ended the year before, and preference was being given to returning veterans. There were about twenty-five of us who decided to reapply the following year—we had been promised admission after a pro forma reapplication—and to mark time we took a postgraduate year, the only time that has ever occurred at Boston Latin School. We studied more Greek, Latin, and other subjects of our choice. Eight of us tried Homer's *Odyssey* in the original Greek in spite of the initial warning and discouragement of our teacher; we surrendered after three days and returned to classical Attic Greek authors.

Growing up, I liked to read about science in the magazine *Popular Science* and later in *Scientific American*. I was especially an avid reader of science fiction. I was always drawing, making model airplanes from balsa wood and paper, and visiting the Boston Museum of Fine Arts and the Museum of Natural History. I read every comic book that came into my father's store while he was still in business. I was hooked on the weekly radio show *The Human Adventure,* which began with Brahms's *Academic Festival Overture* and always dealt with a famous explorer's or scientist's life and discoveries. It was a time when it was safe for a seventh grader to explore Boston on the subway, bus, and trolley and visit the museums, especially since there were no admission fees, except for the Isabella Stewart Gardner Museum, which I could not afford.

I entered Harvard College in 1947. I was able to handle the course material and laboratory time easily because of the seven years at Latin School. My real career interests were archaeology and architecture, but they were quickly shot down by a wise and adored uncle who pointed out the rarity of Jewish archaeologists and architects at the time. With no interest in the law or business, I chose medicine because of the science involved. In 1947 Harvard had curricular distribution requirements for graduation and for honors that had been instituted years earlier by President James Bryant Conant to ensure a broad and balanced curriculum for everyone regardless of their major.

I majored in biology and took courses for honors, which resulted in a lifelong dietary aversion to shellfish and mushrooms. But I had the good fortune to meet Charles Radding, who was a year behind me in the Biology department. I also had my first experiences of designing and conducting laboratory research in both sociology and biology. One of the courses I took for distribution outside my major was "Symbolic Logic" taught by Willard Quine, whose work in mathematical logic contributed to the development of computers. A requirement in the course was a paper on symbolic logic or a paper dealing with probability and statistics. I chose the latter based on the following observation: in large lecture courses (250–350 students), there were always students who pushed their way to sit in the first few rows while others did not care where they sat. It inspired this question: Could there be a correlation between your grade and where you sat in the lecture hall irrespective of how eager you were to sit in the front? At that time in several large courses the seats were assigned serially by alphabet; and the teaching fellows, for reasons I have never understood, had to take attendance. Because of this, it was possible to correlate a student's final numerical grade (converted subsequently to a letter grade) with where he sat. Collaborating with a fellow student, I received permission from Professor Gordon Allport to perform this study in his course "Social Relations." Using regression analysis with slide rule, pencil, and paper, we found that the highest numerical grades were acquired by those in the first five rows of the orchestra and in the first two rows of a five-row balcony in Harvard's huge Memorial Hall. Professor Allport was surprised and said he would look into it further, but probably never did. About twenty years ago the experiment was repeated and confirmed at another university.

In the honors program in biology one had to take a yearlong laboratory-based course in which the student worked on a hypothesis-driven experiment of his own design or that of his supervising professor. I had just completed a course on Mendelian genetics—the double helix was yet to be discovered—taught by a visiting professor, Leslie C. Dunn, from Columbia University. He had brought with him a mutant mouse strain, Trembler, which exhibited tremors at rest and on activity and seizures later in its life span of one year. I had become interested in neuroscience and requested some mice as breeders for a colony. He agreed and I soon had a colony and a faculty supervisor, Professor John Welsh, an invertebrate neurophysiologist, which was as close as I could get to mammalian neurophysiology. At the time, a hot topic in neuroscience was the recording of brain waves and their correlation with epilepsy and other psychopathology. I assembled a recording apparatus with platinum electrodes and devised a surgical technique with a Dremel tool to expose the brain for the recordings. I also used different pharmacologic agents in an attempt to control the seizures and tremors. No positive findings came out of this study, but I had a real hands-on experience with designing and carrying out research and I loved it. To complete the study, Professor Welsh and I went to see his friend Dr. Stanley Cobb, the chief of neurology and neuropathology at the Massachusetts General Hospital (MGH). Dr. Cobb graciously offered to study my mouse brains under the microscope to see whether there were any anatomical abnormalities. He called in his fellow and requested that he perform this study. No neuropathological abnormalities were detected. After I became a faculty member with postdoctoral fellows, I realized the enormity of that request. At any rate, Drs. Welsh and Cobb thought I should publish the negative results, and I submitted the paper to the *Journal of Neurology and Neuropathology*. When it was rejected because of the negative findings, I was already a first-year Yale medical student, and the main reviewer who nixed the paper was my physiology professor. Dr. Cobb, however, believed that the paper should be published, called the editor whom he knew, and the paper was printed. About thirty years later, investigators found that the abnormality was a defect in myelin sheath formation at the point where the nerves to the limbs exited the spinal cord — a sort of multiple sclerosis neuropathy. My familiarity with electroencephalography (EEG) made it possible for me to obtain a paying job as an EEG technician at the MGH for the next two summers. During the summer months between my junior and senior years while I was working as an EEG technician, my fourteen-year-old brother made several visits to the animal facility at Harvard College to check on the Trembler colony. Today's regulations would never have permitted such assistance on my behalf.

That year of research also provided a window into the way some researchers viewed each other. At my interview for Harvard Medical School, the interviewer, a thirtyish physiologist, spoke with disdain about the Trembler project, stating that a morphologic analysis of the brain was a waste of time. Whether this was a stress test or he was serious, I am not certain, but my body reaction I am sure communicated my nonverbal response and ruined the interview. I was invited to interview at Yale, where I had friendly conversations, at the conclusion of which I was offered a place in the class of 1955. Harvard declined to make an early decision, so I accepted Yale, which was the best decision I have ever made or more likely was made for me. Yale School of Medicine — what a way to be educated! Independent study as a graduate student with plenty of faculty guidance and role models. I learned the importance of the doctor-patient relationship from Dr. Paul Beeson, the clinical skills of the diagnostician from Dr. Gerald Klatskin, and the skills for mentorship of students from my mentor, Dr. Elias Manuelidis. I had brought the Trembler mice with me to Yale to continue work with a Yale neuroscientist — a major strength at Yale that has continued to the present. Unfortunately the mouse colony did not survive over that first summer and I had to choose a new project.

I decided to continue with a neuroscience project under the supervision of Dr. Manuelidis. The project was a simple one: What is the origin of the spidery-appearing cells known as microglia present in the brain? They had been an enigma since they were first described in 1920. Microglia are found in excessive numbers following West Nile virus infection. The design was simple: inoculate mouse brains with virus, harvest them at intervals over the course of three weeks, and examine the brains histologically for the presence of these cells. Because West Nile virus was already recognized as a dangerous infectious agent, I was not permitted to work with the cultures. The technicians injected West Nile virus into the brains of normal mice and then prepared the brain sections for me to study under the microscope. It had always been assumed that microglia were a normal constituent of the brain and that they proliferated in response to an infectious agent or other stimuli. I was surprised to find that microglia originated as blood cells that migrated from the blood vessels into the brain tissue and then transformed themselves into spidery-like cells in response to the virus infection. This was a novel observation for its time: the ability of a cell from the bloodstream to migrate into another tissue and transform itself was unexpected. I was urged to publish these data, but I was now a medical intern and had neither the time nor the energy to do so. Dr. Manuelidis included my observations in his book on neuropathology. In 1988, thirty-three years later, my observations on microglia were confirmed by Hickey and Kimura using modern techniques of histochemistry.

By the end of my medical internship in 1956, I had decided that I would become a practicing internist with an as yet undetermined specialty. I enlisted in the army to fulfill my two years of obligation and then resume my residency without interruption. I was assigned to the dispensary in the Pentagon as a general medical officer to provide care to the officers and VIPs serving there. The dispensary consisted of twelve physicians, an equal number of dentists, a small x-ray unit staffed by a civilian, a clinical laboratory, and a pharmacy. The pharmacy was the most important component because the sergeant in charge used to trade aspirin and terpin hydrate with codeine—a cough medicine that contained a significant amount of alcohol—with an air force sergeant for the latest 16mm Hollywood movies that we viewed while on call on evenings and weekends. The air force officers routinely watched these films during their lunch breaks.

About 15 percent of my patients had skin disease. My knowledge of skin disease was limited, and none of my colleagues were interested in skin problems. I convinced the commanding officer to purchase a few dermatology reference books and atlases for the dispensary library for our daily use. My eleven colleagues responded by then sending me their patients with skin disease. I had to refer virtually everyone to consultants in Virginia, Walter Reed Hospital, or the Navy Department. By the time the consultation report returned three weeks later, I had forgotten what the initial rash looked like. However, fate intervened six months before the end of my tour of duty. We were assigned a new commanding officer, who offered us Wednesday afternoons off for continuing medical education. I immediately contacted my main dermatologic consultant, Col. John Reisner at Ft. Belvoir, Virginia, home of the U.S. Army Corps of Engineers, who was overjoyed to have me spend time with him because he was the only dermatologist on the base. I was so impressed with his knowledge of internal medicine, dermatology, and their interrelations that I seriously began to consider dermatology instead of internal medicine as a career. I returned to Yale for another year of internal medicine ($100 per month plus food and laundry) as I had promised the program directors. One of my interns that year was Dr. Gerard Burrow. By the end of the year, after speaking with Dr. Aaron Lerner, who had been recruited to Yale three years earlier to establish a Division of Dermatology, I was convinced this was the career for me. In 1959 I started my dermatology residency and was fortunate to apply for and receive a Helen Hay Whitney Foundation Fellowship in rheumatic diseases that provided a living salary for the second and third years of dermatology residency—

a much needed assist since I was married with a son and a daughter at this point and a third son who would arrive shortly after I joined the faculty in 1962.

In 1959 the Dermatology division was small: two faculty and three residents to cover a private outpatient service two days a week, a hospital-sponsored dermatology clinic three afternoons a week that was also a required rotation for medical students, an inpatient service of twenty-one patients, and consultation service to the rest of the inpatient and outpatient departments. Somehow we managed to cover all these activities. Until the University of Connecticut established a Division of Dermatology in 1980, we saw every patient with a significant dermatologic disorder in Connecticut. Because the state is small, has a nontransient population, and no patient was further than a 1.5-hour drive away, we saw at least one example of every skin disorder ever described in the most comprehensive dermatology textbook; and more importantly, we were able to observe the natural history of these disorders and their responses to therapy over twenty to forty years in many instances. I was always carrying my camera with close-up lens wherever I went. By 1962, the year I joined the faculty as assistant professor, I had all the photographic illustrations I needed for the first edition of my text, *Skin Signs of Systemic Disease,* which was written over the course of the next six years and published in 1970.

Also in 1962, I had read a brief report in the journal *Nature* about a new mouse strain at the University of Otago in New Zealand that mimicked lupus erythematosus. Following a brief correspondence, they sent me three breeding pairs each of the black and white mouse strains that when bred together produced an agouti hybrid that had many of the features of lupus erythematosus. Over the next seven years I established a colony of these three strains and documented their natural history; through backcross breeding I determined the minimum number of genes needed to produce the syndrome; and I studied the transfer of disease from one animal to another through cross-blood circulation by suturing their flank skin together. At this point, I had conducted the investigation as far as I could go, because further studies entailed immunologic approaches for which I had not been trained.

I had always been interested in electron microscopy as an investigative tool. In addition, electron microscopic images for me were aesthetically very pleasing. In 1969 I was eligible for a sabbatical, and I went to the University of Washington in Seattle as a visiting scientist in the Department of Biologic Structure to train with Professor John Luft, one of the leaders in the field. The major side benefits were substantial: my family and I were able to spend quality time together; we learned to ski; and the combination of traveling around the Pacific Northwest, including British Columbia, and the cross-country drives from New Haven to the West Coast and back by two separate routes was an educational experience that was priceless.

After becoming proficient with the techniques of electron microscopy, I needed a project to practice on. I thought I had an easy one. I had been collecting samples of skin from patients with vasculitis, an inflammation of the microscopic blood vessels in the skin, a disorder believed to be caused by deposition of antigen-antibody complexes in the walls of these vessels, based upon a laboratory model in rabbits. No one had yet demonstrated their presence in human cases, and I thought I could be the first. Of course I did not find any deposits, but I quickly realized that they would be present only in the first few days after the onset of the vasculitic rash, and my samples had been obtained too late in the course of the disease. Later, I did find the deposits in samples obtained early in the disease. But much more importantly, I realized that I could not identify with certainty whether the vessel I was looking at was a capillary or a microscopic artery or vein. Each atlas of electron microscopic images I consulted identified the same vascular image as a different segment of the microcirculation. It was clear that electron microscopic criteria for identifying and differentiating the tiny veins from arteries and capillaries in the skin had never been established. This was to be my field of research, because understanding microcirculation would lead to an understanding of many skin diseases.

Over the next twenty years, from 1970 to 1990, our laboratory established the electron microscopic criteria for identifying the venules, capillaries, and arterioles in the skin and underlying fat layer; we demonstrated the three-dimensional organization of the blood vessels within the skin—they were not randomly distributed like wet spaghetti in a shoebox as researchers had believed; and we demonstrated the three-dimensional organization of the different cell types that were the building blocks of these vessels, both in their normal configuration and in their malformations. At first we built models made of paper and string and colored clay, and later we developed a computer system for three-dimensional reconstructions. We established the vascular abnormalities in psoriasis, diabetes, aging skin, and a variety of other skin disorders using the microscope and the computer system. We then began measuring blood flow in these disorders with a laser Doppler instrument in an attempt to correlate their structure with their function, and unexpectedly we discovered a way to begin understanding how the autonomic nervous system controls the cutaneous blood flow. The laser Doppler instrument produced complex wave forms, somewhat resembling those of an electrocardiogram, that we analyzed by Fourier analysis. We were assisted at this point by Professor Rimas Vaisnys from Professor Werner Wolf's department, who later planned to use our observations as an example of the practical application of Fourier analysis in his course on electrical engineering. We now had all the tools to study rheumatic disorders such as lupus erythematosus, scleroderma, and dermatomyositis, as well as other skin diseases. Although the microcirculation was my main research interest and effort, we also were investigating cutaneous T-cell lymphoma as well as collaborating with Dr. Philip Sarrel on the effect of menopause on the skin before and after estrogen therapy. Concurrently, I had been developing a large referral clinical practice and had been assigned responsibility for medical student teaching. It was possible to do these different tasks because of the exceptional talents of my laboratory assistants and our dermatology residents.

However, all this research came to an abrupt halt in 1990 with the change in emphasis at the NIH from pathophysiologic studies of whole animals to a study of the genome. Many of us could no longer obtain funding. Laboratories closed and technical people lost jobs all over the country. From 1990 on, I concentrated on patient care, teaching residents and students, and preparing the third edition of my book, which was published in 1998.

In 1997, a week before Thanksgiving—I remember the exact time—I was running grand rounds, where we examine and discuss the cases of individuals whose skin disorder represents a diagnostic or therapeutic problem. The faculty, residents, and community dermatologists visually examine the patients, none of whom we have previously seen. Questions are not allowed, and we come to diagnostic conclusions as best as we can by visual analysis before we hear the history and results of the laboratory tests from the treating physician and pathologist respectively. As part of this exercise, a dermatology resident describes the skin rash and then develops a series of potential diagnoses. On that particular day the residents were not doing a good job of describing the skin lesions. I was frustrated because I had always pointed out and emphasized the subtle details and the diagnostic features of skin lesions to residents. I had assumed that eventually they would be able to develop a set of visually analytic steps to do the same; instead they were simply memorizing what I pointed out, instead of developing an analytic approach to understand the nature of the skin lesion or rash under consideration. I suddenly had an epiphany. Perhaps they did not know how to begin or complete the visual analysis of an unknown rash because the presence of surrounding normal skin features was somehow confounding. Perhaps if I asked them to describe an object that was totally foreign to them—some object that they had little or no prior knowledge about, so that they had no biases or prejudices—then they would describe every detail in the object because they would not know what was important or not. A painting came to mind, and the seeds of the current observational skills program using fine art were born. After the residents spent a morning at the Yale Center for British Art describing paintings, they performed much better for the next few weeks.

After a series of serendipitous events, beginning with the acceptance and encouragement of this visual training exercise by Dr. Robert Gifford, then dean of students, Jackie Dolev—a first-year medical student—and I designed a study using control and intervention groups with pre- and post-tests that demonstrated the effectiveness of the method by statistical analysis. After publication in *JAMA* in 2001,[1] this exercise became a required course for first-year Yale medical students. Since 1998 at least sixty medical schools in the United States and five abroad (in Taiwan, Ireland, and Great Britain) have adopted the program. The program locally now includes the nursing students, physician associates, and most recently the residents in internal medicine and radiology.

The Koerner Center is the pot of gold at the end of the rainbow: a place where education continues with warm new friendships. I often describe the Koerner Center to friends and family as "Day Care for Retired Professors" when I wish to be glib and facetious, but more seriously, to colleagues as an "Intellectual Candy Store," which it surely is. This exercise of the Intellectual Trajectory emphasizes and confirms how important early childhood experiences, education, and especially serendipitous events are in determining the scope and direction of one's life journey. I believe these Intellectual Trajectories serve a useful purpose in informing young people about career development and demonstrating that life is not a linear path but more of a wandering pathway beset with serendipitous events.

And for us in medical academia, where the metaphor of the three-legged stool is real and tangible — patient care, teaching, and research — the reality of becoming established and hopefully successful is totally dependent upon the unstinting support of spouses and children in the early stages of one's career. My career would not have been possible without the support of my late wife, Muriel, and my three children, Paula, David, and Michael. In addition, Michael as a sophomore at Harvard assembled the hardware and wrote the software for the computer reconstructions. And for the past eighteen years I have had the support of my companion, Marian Wexler.

Thank you for your patience and indulgence in these reminiscences.

Notes

1 Jacqueline C. Dolev, Linda Krohner Friedlaender, and Irwin S. Braverman, "Use of Fine Art to Enhance Visual Diagnostic Skills," *The Journal of the American Medical Association* 286 (2001): 1020–21.