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Reflections on a Career in Pediatric Neuropathology, with a Note of Gratitude

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Abstract

I am honored to be asked by the journal to write this personal essay about my career in pediatric neuropathology—a life of immense satisfaction, meaning, and fulfillment. My motivation to enter this discipline is highlighted, as is my decision to perform brain research in the sudden infant death syndrome, the leading cause of postneonatal infant mortality in the United States today. I also touch upon collaborations, mentoring, and experiences along the way—especially with the light microscope. I close with thoughts about the future of the discipline from my perspective as a lifelong devotee.

May you build a ladder to the stars
And climb on every rung.
May you stay forever young. . .
May your hands always be busy.
May your feet always be swift. . .
May your heart always be joyful.
May your song always be sung.
And may you stay forever young.
Forever young, forever young.

—Bob Dylan, Nobel Laureate, Poet of the Sixties, "Forever Young"

Let me begin by thanking the journal for the great honor and privilege of its invitation to write an autobiographical perspective of my career in pediatric neuropathology. This career was mainly played out in the Department of Pathology at Boston Children's Hospital and Harvard Medical School (1981–present), including now as a fortunate professor emerita. I have thought long and hard about what to say, and to whom, through this gracious opportunity. I have decided to focus on what motivated me to choose and follow a lifelong career in pediatric neuropathology, human developmental neuroanatomy and neuroimaging, and finally brain research in the sudden infant death syndrome (SIDS)—these things that brought immense satisfaction and happiness along the way. These thoughts are directed to the student in us all who seeks to know what makes a rewarding academic career, from one who has been lucky enough to have personally lived it. These thoughts also address how the career discipline—in my case, pediatric neuropathology—combined with personal experiences (involving mother, father, husband, son, family, friends, and mentors) shaped that career into self-awareness, humanism, discovery, and public service. These are all included in the sine qua non, I believe, of the meaningful and happy life. In closing, as suggested by the journal, I comment on what I think are important lessons for the future of pediatric neuropathology from my career perspective.

First of all, to put the story in perspective, you should know that I am a child of the sixties. In 1960, I was 11 years old, and in 1969, I was 20 years old. These were iconic times, as we all know, of wistful "brotherly love" and great turmoil—the backdrop of the formative years for me of transitioning from child to adult. Some of the major historical events of the sixties were the Apollo moon walk; the Vietnam war; the civil rights movement; the war on poverty; the women's movement; the assassinations of Dr. Martin Luther King, Jr., President John F. Kennedy, and Senator Robert F. Kennedy; the introduction of commercially available oral contraceptives; the rise in the use of experimental psychedelics; the first kidney transplant; the general marketing of the polio vaccine; Woodstock; and the emergence of musical icons The Beatles, Marvin Gaye, and Little Stevie Wonder. All of these events played into landing me, like a woman on the moon, in a career in the stellar discipline of pediatric neuropathology. And then there was the singer-songwriter Bob Dylan. It was Dylan who wished for us all, like his son, to stay "forever young." I took this lesson from the poet of my times to heart and followed the career path of pediatric neuropathology because I had an intuition—formed from listening endlessly to Dylan sing poetry, and subsequently found to be true—that it would help me to "stay forever young". . .and all that that means.

I was motivated to enter pediatric neuropathology in large part by truly memorable mentors from early on. Mentors matter. My earliest mentor, not surprisingly, was my late father, Dr. Thomas D. Kinney, chairman of pathology at Duke University Medical School in Durham, North Carolina, starting in the sixties. When I was about 11 years old, my father told me one

Sunday afternoon that he wanted to show me something really exciting that had just come to his department. He took me to the department, deep in the basement of the medical school, as all pathology departments were wont to be back in the day. We walked down a long dark hall and he opened the door at the end, turned on the lights, and said with unbelievable joy in his voice, not lost even upon his 11-year-old daughter, "There it is, an ELECTRON MICROSCOPE!" I had no idea what he was talking about, for all I saw was a wooden kitchen table with a round stovepipe wrapped in aluminum foil going up to a hole in the ceiling. And that's when my father said excitedly, "*That*, Hannah, can blow up a bug to the size of a football field!!" And I remember thinking instantly to myself, "Why would you want to do that? Bugs are scary enough as they are!" But his enthusiasm was contagious, and I was—in some instinctive way—hooked on the microscope at that moment by his passion, his will to learn further and more deeply, and his love of nature. I wanted from then on *to blow up nature*—later focused on the brain—to learn more with the best and the latest tools available. It was his curiosity about the morphology of a bug that hooked me, a curiosity so great that my father wanted to study bugs at the greatest magnification possible at that time, the size of a football field. Here he passed instinctively to me the golden message of the autopsy, a word derived from the Greek αὐτοψία (*autopsia*)—"to see for oneself." Pathology may have been in my genes, but it was in my future definitely from then on: I wanted to see for myself.

What is pediatric neuropathology and why did I choose it as a lifelong devotion? Simply put, pathology, again a term derived from Greek, is the study of suffering ("pathos") or disease, with "suffering" here being synonymous with "disease." Pathology is the science of the causes and effects of diseases, and it represents the bridge between science and medicine, especially with the study of organs and other samples of tissues. Pediatric neuropathology is the study of childhood diseases of the central and peripheral nervous system in the embryo, fetus, preterm infant, postnatal infant, toddler, and child through the adolescent. The tool supreme of pathology, after human insight and ingenuity, is the microscope, the first iteration of which was promoted in the 17th century in Europe. I was guided, I think, to pathology by the physician's humanitarian instinct to alleviate suffering. I wanted to be a doctor for as long as I can remember. At a very young age, my father heard me playing make-believe hospital with my dolls one day, and I called myself the nurse as I bandaged their heads. He leaned over from his ever-watchful chair and said, "You can be the doctor, Hannah." I guess my desire to alleviate suffering came from witnessing the turmoil of the sixties, broadcast on the evening news every night for the first time in history for even a developing small child to see for herself.

Why did I choose to study the human brain, and focus on the pediatric brain in particular, as a lifelong career pursuit? Here, again, mentors mattered. My first real encounter with the human brain came in neuroanatomy class in the first year of medical school at Case Western University School of Medicine in Cleveland, Ohio. I was taught by a brilliant and charismatic neuropathologist, teacher, and, yes, woman, the late Dr. Betty Q. Banker. She rolled out proudly and in lucid and exquisite detail the elegant map of the wondrous human brain in the daily lab—and all the functional directions this map led to, including the pinnacle of human consciousness—and I again was hooked for life. I started out with formal training in a pediatric residency because I wanted to be a pediatrician—I have always loved children, and I was especially fascinated by how they grew and how they developed into sentient adults with self-awareness and full consciousness—a miracle that I wanted so much to understand at the most fundamental level, in order to understand myself. It was the extraordinarily refined and incisive textbook of neonatal neurology by the preeminent pediatric neurologist Dr. Joseph J. Volpe at Boston Children's Hospital that was instrumental in inspiring my focus on developmental neuropathology (1). I came upon his book during my neuropathology training at Harvard Medical School, on the bookshelves of the fellows' workroom. This book told of the trajectories in brain development of neural tube

closure, neurogenesis, neuronal proliferation and migration, synaptogenesis, axonal outgrowth and branching, myelination, and neurotransmitter maturation, as well as their pathologies and mechanisms, correlated and integrated with their clinical manifestations of suffering and disease—all in beautiful text, photographs, tables, and diagrams. Such was the inspiration of this classic book that it led me in my subsequent academic career to study and publish research on the topography and sequences of developmental brain processes in early pre- and postnatal life in health and disease, covering with my colleagues in part oligodendrocyte cell lineage (2), myelination (3–5), neurotransmitter receptor profiles and developmental trajectories (6–10), axonal tract tracing with DiI (1,1′-dioctadecyl-3,3.3′,3′-tetramethylindocarbocyanine perchlorate) in the human fetal brain stem (11, 12), serotonergic neuronal cell positioning (13), and axonal bundle connectivity, the latter combined with human postmortem tractography of neural networks that compose the structural correlates of arousal, awareness, and consciousness (14).

Why did I—with my consciousness formulated in the sixties when so much was at stake—follow the path to perform SIDS brain research? SIDS is the sudden and unexpected death of a seemingly healthy infant in the first year of life that remains unexplained after a complete autopsy and forensic investigation (15). Typically, the infant is found dead in a sleep period, having died during sleep itself or in one of the many spontaneous arousals that interrupt normal infant sleep during the night or a nap. Beginning in the mid-1980s—10 years before the seminal recognition of the association of SIDS risk with the prone sleep position and the initiation of the National Institute of Child Health and Human Development (NICHD)-driven Back-to-Sleep campaign (15) and 15 years after the standard definition was first proposed by the National Institutes for Health for vital statistics, research, and parental counseling—I began SIDS research in my neuropathology fellowship. My overarching hypothesis was that an intrinsic defect in brain-stem sites, which mediate cardiopulmonary reflexes during sleep, in the critical developmental window of the first year of life, results in sudden death when triggered by a homeostatic threat. Our major contribution was to provide tissue-based evidence in SIDS autopsy cases of a disorder of serotonin receptors and other serotonin-related measures in interconnected regions, that is, in a serotoninergic defense network of medullary nuclei that mediate arousal and/or autoresuscitation (15–26). These data suggested that at least a subset of SIDS is due to a serotonopathy, resulting in a failure of autoresuscitation during a sleep period. It should be noted that serotonin receptors are not exclusively involved in SIDS; muscarinic, nicotinic, and GABAergic receptors are also involved in this protective network in alternate tissue sections from the same cases and controls (18, 27–29). These autoradiography studies provided much needed insight as a segue, I believe, into biomarker discovery and, hopefully, future pharmaceutical intervention. Collaborating with the creative SIDS thinker, researcher, and pediatric neurologist Dr. James (Jim) J. Filiano, my first "student-plus-mentor," we put forth in 1994 the so-called triple risk model (16), positing that SIDS results when three factors overlie each other in a Venn diagram: an intrinsically vulnerable infant, an exogenous homeostatic stressor, and a critical developmental period in early homeostasis as the newborn transitions to independent existence from the placenta (16). Jim reinforced to me that some of the best mentors in my career are talented students, to be listened to and heard at all costs.

Tackling SIDS brain stems at the time was extraordinarily frustrating for a pediatric neuropathologist bent upon identifying diagnostic morphological hallmarks of brain-stem disease, since these SIDS brain stems were unrevealing under the light microscope. The exception was of subtle, nonspecific astrogliosis (scarring) mainly in the medulla, as pointed out by the pediatric pathologist Dr. Richard Naeye in 1979 (30) and essentially replicated by us, in my first published work concerning SIDS (31). I was prepared for this phenomenon of central nervous system dysfunction in the face of no identifiable histopathology from my attendance at brain cuttings in my neuropathology training at the state psychiatric hospital with my great teacher and mentor, the late

neuropathologist Dr. F. Stephen Vogel at Duke Medical School. It was Dr. Vogel who showed me, in his dignified, compassionate, and scholarly manner, brain after brain of unfortunate individuals dying at the state hospital who were developmentally impaired in motor function and/or cognition, for example, cases of cerebral palsy or of devastating mental illness, such as schizophrenia or bipolar disease—and yet whose brains "looked normal" grossly and microscopically. He taught me that, to see for ourselves, we had to look deeper with more refined tools. It was another mentor, the late Dr. Alfred Pope at McLean Hospital and Harvard Medical School, a thoughtful, kind, and unassuming neuropathologist, who taught me that neurochemistry was such a tool to probe the structurally intact brain for disease—that such work could be valid in the human autopsy brain, if the postmortem interval and other relevant variables were factored into the analysis. For me, if SIDS was a brain-stem disorder, it was likely quantitative, and it would require new research tools to uncover at the subcellular, molecular, and/or neurochemical level, an idea reinforced by my research mentor in neuropathology, the distinguished developmental neuroscientist Dr. Richard L. Sidman at Harvard Medical School.

In terms of SIDS, it was Dr. Ronald M. Harper at the University of California, Los Angeles, who taught me the biology of sleep/waking and guided my thoughts, along with Drs. Susan Dymecki, Eugene E. Nattie, James C. Leiter, and others, as to how this process may be disrupted in the SIDS infant. My fascination with concepts of arousal, awareness, and consciousness was solidified by the study of a patient in the persistent vegetative state for 10 years, Karen Ann Quinlan (32). Her neuropathological study reminds me that certain patients are mentors, too, and can change conceptual models through single case reports (32). Her case taught me that the structural correlates of arousal and awareness, the bulwarks of consciousness, are separate and able to be parcellated from each other under the microscope and that the thalamus plays an essential role in consciousness. I appreciate the efforts of the late Dr. Martin Samuels (Harvard Medical School), an unsurpassed neurologist and clinician, to think about consciousness in Karen Ann Quinlan and her iconic brain pathologic findings (33). I also have learned in my emerita years that, if you are lucky, younger mentors will still come to you to help with the work, as witnessed by the exceptional neurophysiologist Dr. Kevin J. Cummings at the University of Missouri.

Thus, in my SIDS research career, I, along with many steadfast student-mentors, such as the highly insightful and motivated Drs. Robin L. Haynes, David S. Paterson, Kevin G. Broadbelt, Jhodie R. Duncan, Natasha Zec, and Ashok Panigrahy, introduced and/or applied such research tools as computer-based cell counting and three-dimensional computer reconstructions, including with immunocytochemistry, two- and three-dimensional tissue receptor autoradiography (with my unmatched biochemical mentor Dr. W. Frost White at Harvard Medical School), proteomics, transcriptomics, high-performance liquid chromatography, quantitative Western blotting, and neuroimaging (tractography) to the study of SIDS brains in order to build, stepwise, tissue-based evidence for the serotonergic brain-stem hypothesis in SIDS. I learned from my mentors, including student-mentors, that discovery in neuropathology depended upon far more than the light microscope. Still, I never doubted that the light microscope was the gateway to it all. The basic premise of our work was that the "snapshot" of pathology in tissues in SIDS autopsy cases depends upon biologic plausibility provided by animal and other mechanistic testing, as taught to me by the inspiring and superlative neuroscientists Susan M. Dymecki, MD, PhD, at Harvard Medical School and Eugene E. Nattie, MD, at Dartmouth Medical School, as well as by the gifted and mathematically minded neuroscientist Dr. Benjamin Okaty at Harvard Medical School, who also trained in transcriptomics with the application to SIDS discovery in conjunction with Dr. Robin Haynes (34).

I always believed a particular strength of our work was its solid grounding in careful statistics under the direction of the highly trained and professional statisticians Dr. Felicia Trachtenberg

and Lynn A. Sleeper, ScD. To me, and I offer to you, quality statistics is a research necessity in any quantitative neuropathologic study, to be rigorously attended to with the best collaborations possible. This work also would not have been possible without the help in accrual and adjudication of cases by the renowned pediatric pathologist Dr. Henry F. Krous and his trusted and dedicated research associate Ms. Elisabeth Haas, MPH, in the San Diego SIDS Research Project; Ms. Haas was also involved in data management and autopsy room assistance. The work in SIDS also involved the steadfast commitment and forensic skills of the San Diego County medical examiners. Such are the breadth and depth of collaborators who are essential in working on the seemingly intractable and complex problem of SIDS. I remind students of the fact that work of this import and complexity is not done by one alone and that deep and public gratitude to many is a given. And I would be remiss if I did not thank the NICHD for its incredible long-term support of our SIDS research. I can tell you that the NICHD can be incredibly helpful in focusing research and identifying needs, not just on financial issues. Witness the wise counsel given to me over time by two exceptional NICHD program officers, Drs. Charlotte Catz and Marian Willinger. I was so appreciative of Dr. Catz when a study section reviewer wrote in his/her critique that my plans for SIDS brain-stem studies were a "fishing expedition"—an assessment that is the kiss of death to any investigator. It was Dr. Catz who then said to me, "Yes, Hannah, but remember, you are fishing in enriched waters"—inspiring words that helped keep me going.

But why SIDS research, one may ask? This grounding in a desire to combat SIDS dates back to a transformative experience in my second year of pediatric residency at the Children's Hospital of Philadelphia, a large pediatric hospital that cared for all children, including indigent patients, mainly African American, in inner-city Philadelphia. At that time, residents covered the emergency room at night without hands-on help from attending pediatric staff. I was awakened at 4:00 a.m. by the nurses telling me there was a baby dead on arrival in the triage room and to come immediately. Terrified, I ran there and started CPR with the anesthesiologist who answered the stat call. The babe was a beautiful healthy-looking black boy, with curly black hair, beautifully cared for, without a mark on his body. At the door, his teenage mother and grandmother were standing, holding each other up, watching, wailing out loud in the dark vast void of suffering. Also there, at the head of the bed where the anesthesiologist and I were working on the baby's upper airway, was the Philadelphia policeman, gun at his hip, who rushed the family into the emergency room in his police car, sirens screaming, lights flashing. And then he bent over and said to me, for all to hear, pointing to the acutely bereft mother and grandmother, "They did it, Doc." And in that flash second it all came together, a Venn diagram for my motivation to enter SIDS research—four overlapping circles of what matters most to me simultaneously impinging on SIDS: love of children; desire to alleviate all suffering; will to fight racism, injustice, and poverty (born for me in the sixties); and focus on brain mechanisms. I was convinced as early as then that the brain was key to the pathogenesis of sleep-related sudden death in infants. I resonated with the involvement of poverty in SIDS as a child of the sixties. Of note, SIDS is, among other things, a problem disproportionately affecting the poor and those of health disparities, with the major risk associated with poverty and correlated features, for example, minority status and maternal tobacco smoking and/or alcohol drinking during pregnancy. I emphasize, however, that SIDS affects people of all socioeconomic, ethnic, and racial backgrounds and without known adverse prenatal exposures. It was a well-to-do mother, many years out, who told me that after her daughter died, she climbed into her child's empty crib in the dark for many nights after the death and lay for hours frozen in limbic pain in the fetal position. The suffering of SIDS is universal and lifelong. I vowed then, in the dawn in the pediatric emergency room in Philadelphia, that if ever I were able to do medical research, it would be to understand the basic underpinnings of SIDS with the goal to eradicate the problem once and for all. This experience was foundational for me in following a career path that

involved research in SIDS in the American Indians in the Northern Plains and the Cape Coloureds in Cape Town, South Africa (35–38), two socioeconomically disadvantaged populations with SIDS rates twice that of the white population. It also inspired me to cofound Robert's Program in Sudden Unexpected Death in Pediatrics for care of the bereaved families of all backgrounds, including genetics and autopsy and neuropathology review, with the deeply empathetic, trailblazing palliative care physician Dr. Richard D. Goldstein (39), at Boston Children's Hospital. I, a child of the sixties, call this body of work "sociological neuropathology," a field that brought great happiness and satisfaction to me as a pediatric neuropathologist. This work was to "be dissolved into something complete and great. When it comes to one, it comes as naturally as sleep" (40, p. 18).

I offer some thoughts about choosing a career in pediatric neuropathology today. Remember that the classic microscope is key—to see for oneself—but importantly represents now the path to all of the state-of-the-art cellular and molecular tools, for example, "omics." We are now in the Age of Omics and the Molecular Autopsy. But the place of the light microscope has not been supplanted in this new age. Gratifying personally for me is seeing one of my student-mentors, the biochemist Dr. Robin Haynes, take over leadership in the laboratory with great focus and skill upon my retirement in 2018. Robin has taken the research to new and original heights in the molecular autopsy—a wish for the future research direction with the use of new and modern omics merged with classical anatomic neuropathology in the toolbox for the 21st-century pediatric neuropathologist (23, 34). Cases in point of our ongoing reliance upon the light microscope as a first pass are our histopathologic observations of dentate gyrus dysplasia in the hippocampus in SIDS and SUDC (sudden unexpected death in childhood) deaths with the compassionate and unparalleled pediatric neuropathologist and SIDS researcher Dr. Dawna D. Armstrong at Baylor College of Medicine, Houston, Texas, and the thoughtful student-mentor and now neuropathologist Dr. Marco Hefti at the University of Iowa (41–46). The microscopic findings in the hippocampus in conventionally stained tissue sections in some SIDS cases mimic those seen microscopically in temporal lobe epilepsy, leading to the possibility that SIDS is a heterogeneous disorder that is composed of more than one "undiscovered" disease process. Indeed, another SIDS subset may involve the generation and propagation of a sleep-induced, fatal, first-time seizure, similar to sudden unexplained death in epilepsy. We also demonstrated that this same hippocampal finding is present in toddlers who die suddenly and unexpectedly. This observation led us to suggest that some underlying "causes" of sudden death occur over a spectrum of ages in childhood and are not necessarily restricted to the first year; rather, there is a wider window of vulnerability. Much research remains to be done to determine the role of hippocampal pathology in sudden death in infants and children and the potential relationship between brain-stem and hippocampal pathology in the same SIDS infants.

Another avenue for discovery by pediatric neuropathology is the link with modern neuroimaging in the autopsied human brain. I believe this convergence of neuropathology and elegant tractography and graph-based mathematical theory will bring a renaissance to anatomic neuropathology, with the combination of pathological markers and tractography. Neuropathology importantly plays a key role in validating neuroimaging. This powerful technology will allow for the in-depth analysis of defective neural networks in the human brain directly, as suggested by the network-based autopsy (14) developed by my student-mentor, the ground-breaking neurologist and neuroimager Dr. Brian L. Edlow, Harvard Medical School; my fellow outstanding colleague in pediatric neuropathology Dr. Rebecca D. Folkerth, Office of the Chief Medical Examiner, New York City; the quick and committed Mr. Mark Olchanyi, Massachusetts Institute of Technology–Harvard Medical School doctoral candidate; and the creative neuroimagers Drs. Roxane Licandro and Lilla Zollei in this new age of brain networks in neuroscience.

I would say that, in 2024, it is no longer accurate to speak of SIDS as a mystery. Noam Chomsky divided mankind's ignorance into "problems and mysteries." To quote him: "When we face a problem, we may not know its solution, but we have insight, increasing knowledge, and an inkling of what we are looking for. When we face a mystery, however, we can only stare in wonder and bewilderment, not knowing what an explanation would even look like" (47, p. ix). The last five decades of SIDS research have given us some insight, I believe, as to "an inkling of what we are looking for" and rational hypotheses to pursue with scientific foundations through the combined efforts of pediatric neuropathology, pediatrics, epidemiology, physiology, genetics, omics technology, and basic science. There is now a generally accepted standardized definition of SIDS: the sudden and unexpected death of an infant in the first year of life that remains unexplained after a complete autopsy and forensic investigation (48). Yet, there is still plenty for the upcoming student to do upon entering pediatric neuropathology, particularly in SIDS research and that of other brain disorders that plague children and may not leave an anatomic trace, for example, autism, cerebral palsy, epilepsy, and neurodevelopmental delays. The Global Action and Prioritisation of Sudden infant death (GAPS) project alone lists today at least 10 top priorities in SIDS research that span from brain anatomy and physiology via basic science and genetics to social and cultural factors influencing adherence to safe infant sleep messages via behavioral psychology and epidemiology (**https://www.lullabytrust.org.uk/research/gaps-project**). We still have a ways to go to understand the fundamental causes and mechanisms of sleep-related sudden death in SIDS and SUDC, to provide the means to identify the living infant at risk, and to potentially provide specific pharmacological interventions to prevent death in the identified infant, as delineated in a call to arms published by our group in a commentary in the *New England Journal of Medicine* (49). Our long-term goal is to generate causal hypotheses in SIDS from evidence based directly in human SIDS tissue analysis for further in-depth study, accompanied with mechanistic testing in animal models. If asked, I would like it to be said of my work that I helped demystify SIDS with hypotheses-driven, tissue-based evidence garnered by the scientific method.

In closing, I end with this last thought—pediatric neuropathology is truly a "ladder to the stars," built to make one stay "forever young"—through imagination, service, scholarship, and creativity. I have met at every rung of this ladder many committed, kind, and thoughtful mentors, students, and colleagues who are too many in number to name in the limited space provided here. Please know that I am grateful to you all and thank you for your many contributions. And I thank the many SIDS parents, young-adult SIDS siblings, and SIDS grandparents I've encountered—mentors who have taught me what "forever young" means with the loss of a precious infant.

This career perspective is dedicated to Joel and Susan Hollander, two SIDS parents who mentored me in what SIDS truly means after the loss of their beloved daughter Carly Jenna to SIDS more than three decades ago.

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