Satisfactions and Uncertainties That Frequent an Extended Life

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EDITORS’ INTRODUCTION

The following reminiscence by Stephen Vogel is the second autobiography in a series published in the Journal of Neuropathology and Experimental Neurology. These have been solicited from senior members of the neuropathology community who have been noted leaders and contributors to neuroscience and to the American Association of Neuropathologists and have an historical perspective of the importance of neuropathology in diagnosis, education, and research. It is hoped that this series will entertain, enlighten, and present members of the American Association of Neuropathologists with a better sense of the legacy that we have inherited, as well as reintroduce our respected neuroscientists as humans having interesting lives filled with joys and sorrows the same as all of us.

MNH, RAS

The satisfactions and uncertainties that frequent an extended life are often inadequately portrayed in words (Fig. 1). Perhaps it is sufficient, therefore, at the onset to merely state that I would not exchange those of my life for extended facsimiles.

I chanced upon this life shortly before sunup on September 29, 1919, in a modest second-story apartment over a 5- and 10-cent store, which in turn, defined the center of Middletown, Delaware, a sparsely populated farm town. Present at the time were my 2 parents, my brother Karl, aged 16 months, and Dr Vaughan, the only practitioner in Middletown. He did not tarry long for it had started to rain.

My parents were high school teachers; they were firmly grounded in the ethic that recognizes and unfailingly portrays a sharp and unyielding line between what is right and what is wrong. My mother was of Scottish extraction. She taught high school mathematics. Her father was a physician who died in the care of others; at the age of 94 years, he was still fulfilling the responsibility of a medical house call in the farmlands of Illinois. My father had inherited a talent for the hard sciences, namely physics and chemistry. In the agrarian milieu of Delaware, he was also called upon to instruct in agriculture. My brother inherited my father’s aptitude for chemistry and became a talented chemical engineer.

In the early days, we traveled to school as a family unit as I was enrolled in the first grade at age 4 years, soon to become 5 years old. The early days, weeks, months, and even whole years of education seem not to retain a place in my memory. However, it became quite a transformational event when at age 10 years, my family bought and moved to a sizable farm 6 miles south of Middletown. It had no postal designation but bore the flighty identification of Blackbird. My father continued to teach in Middletown and my mother in Smyrna, 6 miles to the south. She taught high school mathematics: algebra, trigonometry, solid geometry, and calculus, with absolute precision, as is inherent in the phrase “2 + 2 = 4, no more and no less.”

The farm of approximately 110 acres encased a large lake and a considerable track of forests. I spent many hours in and on the lake as well as tramping through the woods in search of nature’s creations. It was quite early one morning, the mist was still rising from the lake, when I caught a sizable bass and admired its attributes that permitted life in an aquatic environment. I returned the bass to the lake. I saw a small frog on a lily pad and recalled that as a tadpole, it began life aquatically, soon to become aerobic. I caught a snapping turtle, a life in a box that spent winters beneath a layer of mud.
and then was free swimming and aquatic throughout the remainder of a calendar. I saw a sparrow in flight, a life supported by wings of feathers. Does life itself create a weight for the body? The weight of the bird is not diminished by death. I saw a large water beetle that had no recall of the past or perception of the future. I saw a centennial oak tree whose broad trunk housed a family of wood ducks. For decades, it had stood motionless with life unbroken from its origin in a minuscule acorn. As I rowed to the shore, I recalled the complexity and diversity of life, and I realized that my life, as all others, seemingly had not come into being merely by chance. I acknowledged the presence of a Creator, and then walked home secure, knowing that life was created and protected intellectually. I felt secure.

My brother and I grew into farm chores. Karl was by nature a tinkerer oriented toward instrumentation and machinery. He acquired a secondhand bicycle whose tires had lost their usefulness. He filled them with a mixture of flour and water. The bicycle marked its path with streaks of whiteness. He filled the tires with sand and the bicycle became stationary. I tended the chickens, a large flock of ducks, and several beehives. I incubated state-provided pheasant eggs, raised the chicks, and released them for propagation. On occasion, I milked one or both of our cows.

In the fall of 1937, my brother and I matriculated into Villanova College, now Villanova University; Karl entered the School of Engineering, and I entered the School of Liberal Arts, with philosophy as my major. My regular courses included history of philosophy, logic, cosmology, Latin, and a foreign language; I took French. In addition to that, in accord with my thoughts about becoming a teacher, I took courses in the School of Engineering, and I entered the School of Liberal Arts, with philosophy as my major. My regular courses included history of philosophy, logic, cosmology, Latin, and a foreign language; I took French. In addition to that, in accord with my thoughts about becoming a teacher, I took courses in advanced physics and chemistry.

It was toward the middle term of my junior year when without any thought or expectation that that day would have any impact on my future, I crossed the hall to visit a close friend, also a junior student, Bob Schisler. He was a member of the premed school. Without forethought, I asked, “Do you really want to become a doctor? They are called out of bed at all hours of the night and are frequently sued by their patients.” I do not recall his answer, but shortly thereafter, he transferred out of premed courses into the business school.

The regrettable event of Pearl Harbor occurred in December of my freshman year. With its occurrence, the male students who were physically qualified were inducted into the Army or Navy. I was pleased to wear the Navy blue through the entirety of my 4 years of medical school.

As previously suggested, I have received many “wind-blowen gratuities” in my life. In my mind, one that stands out, perhaps above the others, occurred just shortly before the beginning of our sophomore year, the year of focused attention upon pathology. For reasons clearly not based solely on academic standing and never made known to myself, another student, John Miller, and I were approached by a member of the dean’s office and offered the opportunity to use a small suite of rooms through the course of that sophomore year. The suite was on the first floor of the Pathology Institute, a very large building adjacent to the university hospital. This building housed the Department of Pathology, the clinical laboratories, anatomical diagnostic laboratories, the teaching facilities for pathology, and numerous research laboratories. Our job was to serve as dieners for the night and weekend autopsies, of which there were quite a few. We received further compensation through the permission to eat without charge in any of the medical center’s dining halls. Autopsies were commonly performed by the senior residents in pathology but also, perhaps in equal numbers, by senior faculty members. Just as I had been fascinated by the diversity of life as created in nature in my earlier years, I now had the opportunity to see the significance of its curtailment as it related to human situations.

Dr Harry Goldblatt was a faculty member who was much interested in renin, as created by renal ischemia and inductive of hypertension. His invitation to serve as the anesthesiologist for his dogs on weekends was an invitation to a reasoned discussion about the philosophy of how one acquires useful information through research methods. Dr Howard Karsner was head of the Department of Pathology. He lectured frequently and had written the textbook used in the classroom. Throughout the year, I saw him only once in the autopsy room. It was known that his interest was to a major degree centered upon the functional tumors of the endocrine system. One evening, I was notified that an autopsy permit had been received by the front office, and accordingly, I prepared the body for autopsy. Clinicians were accustomed in that period to arrive shortly after the appearance of the prossector. The elevator was heard to approach the fourth floor. In street attire, Dr Karsner stepped off. He came to the table and said, “I see the permit restricts the examination to an incision not greater than 8 inches.” The medical chart had defined that this patient was considered to have a tumor of the right ovary, and that she had died unexpectedly of a pulmonary embolus. Without putting on a gown, Dr Karsner addressed me, “Well, go ahead and make the incision.” I did without difficulty and also without difficulty removed the tumor and placed it on the cutting board. Dr Karsner added, “Well, cut it.” I did, and he said, “What do you see and what does it mean?” And then he added, “Let me clarify, I did not say what do you know about ovarian tumors?” I described the physical characteristics of the mass as best I could and suggested that perhaps it was a benign granulosa.
cell tumor. Dr Karsner said, “Son, no matter what branch of medicine you enter, when you approach a patient and have the opportunity to see a disease process, always ask yourself, ‘what do I see and what does it mean?’” He then added, “this evening, you have the privilege of seeing a disease process. It is a privilege granted by the unfortunate circumstances of the patient and through the generosity and understanding of the family.” On many occasions, I have followed Dr Karsner’s suggestion even that which he added when he apologized and said, “I have a dinner date and must leave early.” Then he added, “Son, I hope you stay in pathology.”

Although the world war was still ongoing as my class approached graduation, I applied to the Navy for a 2-year leave of absence indicating my hope to take a 2-year rotational internship. My request was granted, and I interned at a large county hospital just above White Plains, NY. During that period, I acquired Dr Kinnier Wilson’s 2-volume text of neurology and was fascinated by the challenges of the central nervous system. I followed my rotating internship with 2 years of general pathology at this same county hospital and then followed this with 3 months in the laboratory of the Neurological Institute in Montreal. I had an opportunity to experience the operative philosophy of Drs Penfield and Cone. Understandably, they viewed a brain tumor as an unfortunate living substance, rooted in the normal brain with margins ill defined radiographically, as well as by direct vision or electrical stimulation. I was called upon to add frozen-section assessments of the boundaries between tumor and the normal brain. Again in this period, I frequently asked of myself, “what do you see and what does it mean?”

In 1948, I began a residency at New York Hospital-Cornell Medical School. Dr John Kidd was head of the Department of Pathology, and Dr Louis Stevenson was the neuropathologist under whom I studied. He had been a previous student of Dr Cajal. Dr Brunson Ray was the head of neurorsurgery. He had served as the last trainee of Dr Cushing.

In 1952, at the onset of the Korean War, I was inducted into the Army. I was stationed briefly at Fort Sam Houston in Austin, TX, and then transferred to the School of Aviation Medicine to be assigned to the Division of Radiation Biology. That laboratory was on the campus of the University of Texas and was headed by Dr T.S. Painter, prior president of the University. I had the responsibility of the Pathology Division. The Air Force, then under General LeMay, had expressed a desire for inquiries into the feasibility of an atomic propelled plane to accommodate the broad expanse of the Pacific Ocean. The design of the airplane placed the crew far forward with the reactor located in the extreme tail. Shielding against radiation had priority for much of the intervening space. The question posed to pathologists was, “what forms of radiation emitting from the reactor (x-rays, gamma rays, thermal neutrons, protons, etc) would have the greatest deleterious effect (relative biologic effect) upon the brain and bone marrow of the crew?” 

The nature of the shielding would be defined by this determination. Dr Webb Haymaker, then head of Neuropathology at the Armed Forces Institute of Pathology, was a member of the advisory board. He had previously drifted primates beneath balloons over Canada at an elevation of 80,000 feet, an elevation above the shielding of the earth’s atmosphere. The intent was to define the effects of high-energy particles upon the central nervous system. Throughout the Texas studies, the aeronautical engineers frequently made the subdued statement, “this thing will never fly.”

The Radiation Biology Laboratory had a sizable colony of Rhesus monkeys and a few chimpanzees. Postmortem studies revealed an occasional incidental finding of salivary gland virus infection in the chimpanzees. Dr Henry Pinkerton, Chairman of Pathology at St Louis University, brought the recently isolated human virus to Texas for injection studies in the remaining few chimpanzees. The evidence confirmed susceptibility to the human strain of the virus. After 2 years, it was widely accepted that the aeronautical engineers had predicted the outcome of the aeronautical project, and federal support was then abandoned.

I returned to Cornell in 1955 with full responsibility for the service and teaching of neuropathology. In this interval, I had also further enlarged my family to a total of 5 sons. Subsequently, my oldest son became a lawyer, two became pathologists, one a horticulturist, a radiologist, and a daughter, born several years later, who was to become a veterinarian.

When I returned to Cornell, I again received a windblown gratuity. I was offered a technician, truly an associate, by the name of Lilo Kemper, who greatly enhanced the technical skills and scientific judgments of my laboratory for 3 decades until retirement.

Early in that period, I had the opportunity to apply Dr Karsner’s advice, namely, to approach a medical problem with the following format, “what do I see and what does it mean?” The case was an example of anencephaly. The cranium was lacking in its formation; the eyes were normal in appearance and in their anatomical position and structure. The hemispheres were disfigured, grossly “cerebrovasculosa.” Rich plexuses of small thin-walled vessels lay within the leptomeninges, particularly at the base of the cerebral mass. The carotid arteries did not physically enter the cranial vault. “What does it mean?” Because the anlage of the eyes are seeded during early embryologic development, laterally in the temporoparietal cortices from whence they move forward into their orbital facial position, one gains assurance that the anterior portion of the neural tube has assumed a normal midline position, and presumably, there has been fusion and closure of the neural tube. Because internal vascular pressure defines the degree of smooth musculature endowment in blood vessel walls, its absence in the leptomeningeal plexuses, combined with the absence of the carotid arteries in the cranium suggest that a regressive state of ischemia developed in the area of the anterior portion of the neural tube.

At that time, Dr Alex Burn was a senior member of the Rockefeller Institute, with interest in the clinical expression of Wilson disease. The proximity of New York Hospital defined a service relationship between the 2 institutions, and autopsies were performed in the Department of Pathology at the New York Hospital. Tissues from the lenticular area of the brains of patients with Wilson disease revealed a marked curtailment in oxidative respiration. This did not explain the normality of respiration by splenic tissue, where the levels of copper notably exceeded those in the brain or...
liver. Furthermore, the addition of splenic tissue in a 1:1 nitrogen ratio with the neural tissue sharply lessened respiratory curtailment. A small polypeptide recovered from the splenic tissue was discovered to have substantial chelating properties for copper.

In 1961, I accepted an appointment at Duke University again, with supervisory responsibility for teaching and clinical services in neuropathology. The Neurosurgery Department consisted of a senior staff composed of Dr Barnes Woodall, Dr Guy Odom, and Dr Blaine Nashold. The question was carried forward, “how do natural biologic systems that depend upon tyrosinase, a copper-dependent enzyme for melanin production, escape toxicity by copper?”

The ink gland of the squid was an inviting model, but the distance to the North Carolina coast, the early morning departure of shrimp boats, and the need for viable squid made that model impractical. We focused our attention upon the mushroom Agaricus campestris. Although it did not concern an approach to a medical problem directly, we again followed the axiom, “What do you see and what does it mean?” We examined the gill tissues by electron microscopy, noting that the basidial cells are the spore-producing cells of the mushroom and that they surface the mushroom gills aligned as palisading tall columnar forms. From their apices are derived 2 spores per cell, hence the designation Agaricus bisporus. Through the entirety of the interval of maturation and early liberation of the spores, the undersurface of the mushroom cap is covered entirely by a substantial membrane that is bound to the stem of the mushroom. It stretches intact across the entirety of the lower surface of the gills to gain firm attachment to the circumferential edge of the mushroom cap. Thus, in the interval during the prodromal process of sporulation, the velum totally shields the gill tissues. It can be excised aseptically, and the organelles can be separated from the gill tissue by centrifugation, free of bacterial contamination.

The mitochondria, as evidenced by electron microscopy, possessed prominent amounts of DNA, seemingly in notable excess of that which had been recognized previously, and only in neuropsila. The mitochondrial preparations were suspended in nutrient broth and placed in slender dialysis tubes that in turn were submerged in a solution of electrolytes comparable to those of the gill tissue. The cylinders were incubated at 56°C, the optimum growth temperature of Agaricus. Thereafter, the contents of the tubes were examined during a period of a few days, and assays were made of protein content. Mitochondrial forms were counted per volume. The structure of these organelles was assessed by electron microscopy. An increase in protein provided suggestive evidence of metabolic activity. Enhanced numbers of mitochondrial figures that possessed a membrane that stretched intact across their equatorial segment provided evidence of binary fission. Together, these findings suggested functionality of the mitochondrial DNA with division by binary fission, all supported by mitochondrial nucleic acid.

The spores of Agaricus are remarkable forms of life. They are totally devoid of metabolic activity. Even after a period longer than 100 years, they possess the potential to reexpress activated functions of life. One asks by what methods is this dormancy created and by what means is reactivation accomplished? These questions have been approached previously and generally attributed to simple dehydration and rehydration. We noted that there was a decline in the metabolic activity in the gill tissues as the mushroom approached the period of accomplished sporulation. This suggested the possibility of a metabolic inhibitor in the gill tissues that curtailed the functional activity of the nucleolus and/or the cytoplasmic organelles before their entry into the spore. A small polypeptide, γ-1-glutamyl-4-hydroxybenzene, was identified within the gill tissues of the mushroom, and the compound was synthesized. It was unstable in aqueous solution but was completely stable when lyophilized. It was activated by tyrosinase to function as a broad metabolic inhibitor, presumably capable of inducing the dormant state of the spores of A. bisporus. Upon injection into black mice, melanocytes of hair follicles were destroyed, and the mice lost coloration. Pigment cells of the sclera of the eyes lost their normal peripherally derived melanin while retinal pigment was preserved, that is, neuromelanin was well preserved. Regrettably, the growth of human melanoma transplants into the skin of nude mice was not notably affected by intramuscular injection of the inhibitor.

In the early 1970s, Dr Webb Haymaker assumed the directorship of the Biologic Division of the National Aeronautics and Space Administration and supervised the laboratories at Moffitt Field in California. He entertained continued concerns for the potential harmful effects of high-energy particles (cosmic rays) upon the central nervous system of astronauts during prolonged space flight. Preparations were ongoing for the Apollo 17 flight to the moon. I was offered a consultantship and joined in the early plans for design of a totally self-sustaining small chamber that would house desert mice during a 13-day flight to the moon. High-energy particles are the nuclei of atoms, as we know them here on earth, and as they extend through the entirety of the atomic scale. The electrons have been stripped from the nucleus, presumably most often while located on a planetary body in our solar system, such as the sun. They travel at the speed of light through space. They are largely shielded by the earth’s atmosphere but can easily penetrate a space vehicle. Shortly before the Apollo flight, an unfortunate incident occurred that caused the death of several astronauts before launching of the space vehicle. Dr Haymaker and I were instructed to establish a "contingency laboratory" at the University of Hawaii to provide, if necessary, a reference biologic system in the event that the Apollo flight had to abort for medical reasons during the early orbital interval. The space vehicle circled the earth several times, and then redirected its course to the moon. Dr Haymaker and I moved to American Samoa to be near the recovery site. I can state that Dr Haymaker was without question the most intellectually and socially stimulating person with whom I have had the opportunity to be associated.

Preparatory to the flight, there was the assemblage of a novel dosimeter that was surgically placed between the dome of the mouse’s skull and the overlying scalp. The dosimeter consisted of 5 alternating layers of cellulose nitrate and lexan, with a combined size approximating that of a small...
fingernail. The plastic wafer would be softened by the passage of high-energy particles. The softened courses would constitute slender columns through the 5 layers of plastic. These layers then could be individualized and etched briefly in caustic solutions to reveal cortical indentations. Comparison of the topography of the conical etchings, the position of one to another, and the diameters of their bases would yield relevant information concerning the trajectory of the particles, their intrinsic energy, their molecular constituent, and their probable point of stoppage. During flight, each dosimeter encountered approximately 70 high-energy particles. The brains were sectioned coronally in toto and histologically examined in relation to the trajectory of the particles. The time of killing of the animals was carried out close to the time of recovery to be in agreement with the concept that it would provide more meaningful information, that is, actively recognize degenerating neurons rather than to be called upon to assess suggestive evidence of an absent neuron or group of neurons.

As characterized by many first experiments, the results relative to the brain left open questions and had to await a degree of confirmation from other sources. As one scanned along the expanse of the epidermis, however, one’s vision encountered a number of segments of the epidermis, over the width of 1 to 2 cells that were completely necrotic. The epithelial cells on the shoulders of these lesions showed morphological evidence of injury, notably the presence of pyknotic nuclei and the occurrence of deeply eosinophilic cytoplasm. The underlying dermis often contained a scattering of a few mononuclear cells, suggestive of lymphocytes. The epidermal lesions were in suggestive conformity with the topography of the patterns derived from the etched wafers. At this point, there was only equivocal information that had been assembled in relation to the fundamental question; namely, will high-energy particles destroy biologic cells?

Dr Haymaker and I were then sent to Cornwallis Island, which geographically neighbors the north pole. The intent was to assess the feasibility of a high-altitude balloon flight circulating the polar areas. Here, cosmic rays are encountered in concentrations enhanced by the magnetic forces of the earth. I wandered out one day over Cornwallis Island hoping, but not expecting, to see musk ox. The rocky ground was largely covered with ice and snow; it was August. I came upon a small plant tucked in a rocky crevice. It was in bloom with an inconspicuous yellow flower. I recalled earlier expressions of the complexity and diversity of life, as noted many years earlier and then had concluded that life is not a matter of chance. Thus, accepting an intellectual origin of life, the findings on Cornwallis Island, with its ice and snow, further characterized the Creator as sensitive to the beauty of His own creation. Similarly, in the tale entitled, “The Adventure of the Naval Treaty,” Sir Arthur Conan Doyle speaks of another time, through the voice of Sherlock Holmes, that also concerned an isolated flower, and thus provided the quotation: “Our highest assurance of the goodness of Providence rests in this flower, placed in a barren location with little chance of recognized adornment, except the satisfaction by the Creator Himself.”
Back to a family that consisted of 5 sons and soon to have the adornment of a daughter, again, a welcomed call from Dr Haymaker with a message, “we need to go to Paris, someone there has done a very interesting study.” In short, this someone had elevated a balloon above 80,000 feet, which, as previously stated, is essentially above the shielding of the earth’s atmosphere. To the balloon was attached a gondola in which were young black mice. Upon recovery, the investigator merely housed the mice under observation. For 2 weeks or so, there appeared lesions scattered randomly on the skin. Some had a central nonpigmented hair, surrounded perhaps by a few other hairs without pigmentation. Other lesions had an absence of one or several hairs in a very focal area surrounded by hairs again that were lacking in pigmentation. This observation constitutes a natural dosimetry. It points directly to the potential harmful effects of high-energy particles on the structural integrity, not directly of the brain, but rather on the epithelial cells of the skin because melanocytes are more sensitive to radiation than keratinocytes.

Dr Haymaker had overtures from Russian scientists to place mice on earth-orbiting rockets that were to be launched. One launch was to be separated from the other by a year. The first year, the dosimeters were placed in the position where the mice would be housed on the second year. The dosimetry, as disclosed by the American dosimeter, varied significantly from the dosimetry records of the Russian instrumentation. The decision was then to focus upon dosimetry rather than the biologic problem during the second launching.

It has been unquestionably the greatest satisfaction in my life to see creativity springing forth among my children and, in a similar vein, to have observed the same occurrence in many individuals to whom it has been my privilege to instruct during their careers of medicine, specifically in the area focused upon neuropathology (Fig. 2).

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