

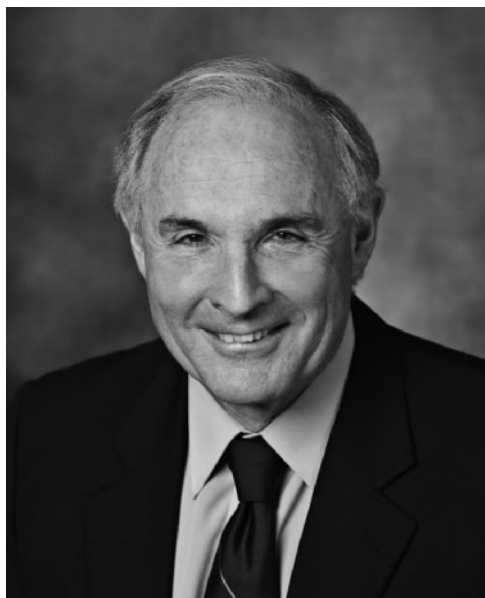
Autobiography Series: In Search of Knowledge and Joy: My Life as a Neuropathologist

Samuel K. Ludwin, MD

EDITORS' INTRODUCTION

The following reminiscence by Sam Ludwin is the 15th 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 (AANP) and have a historical perspective of the importance of neuropathology in diagnosis, education, and research. We hope that this series will entertain, enlighten, and present members of the AANP 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 and allowing them to present their lives in their own words.

MNH, RAS



Samuel K. Ludwin, MD

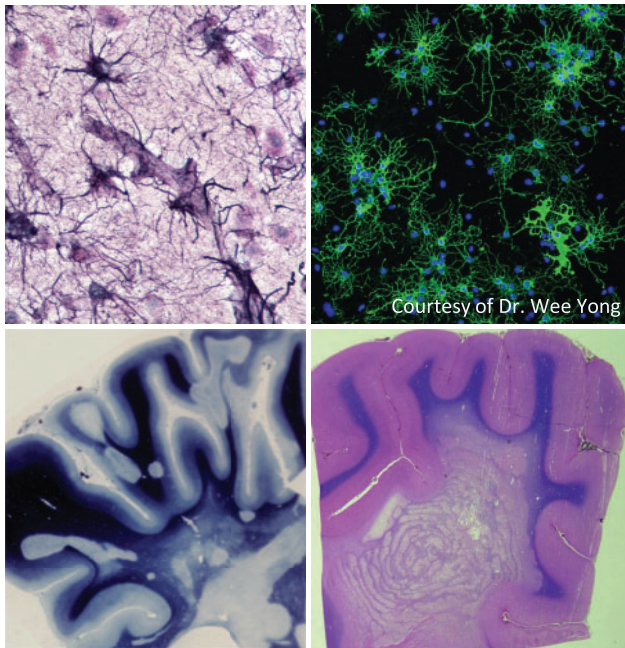
When then Editor, Ray Sobel, first approached me about writing an autobiography for the *Journal*, I was very skeptical for two reasons. My first thought was that only old dogs write autobiographies. I quickly realized with a certain degree of resignation, that I probably am already

one of these, so that was no excuse. My second was to ask who would be interested in reading this. This was much more difficult to answer, but it gradually dawned on me how wonderfully satisfying a career in neuropathology has been to me. There were three elements to this: first, the beauty, the fascination and the constant evolution of the subject in the largest sense, secondly, the opportunities it has provided for me to pursue multiple areas of interest, and finally, perhaps most importantly, the associations with numerous mentors, colleagues and students who have guided me, taught me and enhanced my professional and personal life so much. This essay is written to pay tribute to these elements, and to those who have been associated with me over the years.

WHY THE APPEAL OF THE NEUROSCIENCES AND NEUROPATHOLOGY?

For those of us in the neurosciences, the brain, of course, holds special attraction. Although the study of other organs shows us important, often complex function, the study of the brain, at an almost spiritual level, goes further and explores how our brains define who and what we are, what makes us think, learn, communicate, and form relationships. Deep age-old questions and valid across most species, these merge the domains of science, philosophy and religion. Despite enormous progress in understanding the brain, through advances in genetics, cell and molecular biology, development and imaging, these questions retain mysteries that may take generations to solve. However, at the same time, our knowledge of the structure and physiology of the brain has shown us the wonderful precision that governs the development, placement of cells, tracts and nuclei, by which we can assess many aspects of the state of health or disease. This tension between precise knowledge and fathomless uncertainty and ignorance, may help explain this attraction. Secondly, the structural order is a physical and visual display of beauty. The images made using 19th to early 20th century silver and gold staining methods, together with the newer ones using immunochemical methods could grace many art galleries (Fig. 1). Even the images of diseased brains can be visually arresting, even while we recognize the diagnostic implications (Munch's paintings, while disturbing, are still great art).

One of my favorite *New Yorker* cartoons shows a very bored starlet, listening (sort of) to a greasy agent who is trying to persuade her to accept a movie role where she



Courtesy of Dr. Wee Yong

FIGURE 1. The beauty of neuropathology: Top: Normal astrocytes in situ, silver-stained (left), and oligodendrocytes in culture, stained with O4 (right). Bottom: MS with old white matter and cortical lesions, and shadow plaques, Loyez stained (left). Baló's concentric sclerosis (right).

becomes a famous neuropathologist. This may reflect the way many people regard our subject as esoteric or an object of humor rather than glamour. However, I am always comforted by the words of my mentor, Lucien Rubinstein, who declared that neuropathology was the string quartet of medical specialties, “The Lowest Form of Entertainment, but The Highest Form of Art.”

MY EARLY LIFE AND (? POSTNATAL) DEVELOPMENT

I was born in Johannesburg, South Africa, at the end of World War II, the son of a Russian father and a Lithuanian/Polish mother who had emigrated from Europe to escape the impending onslaught of anti-Semitism in Europe. The timing of their moves was fortuitous because many of their relatives perished in the Holocaust. My father worked for many years in his uncle's grocery business until he entered medical school and became a general practitioner in his early 40s. My mother became a teacher. I was the second of four children. My younger brother is a nephrologist in Canada, and his twin sister, a clinical psychologist in Scotland. Our older sister, a homemaker, emigrated first to the USA and then to Israel.

Growing up in apartheid South Africa, one of the most racist societies in the world, had a profound effect on my development. The humiliation and poverty of the Black population ensured that many of us were highly politicized at an early age, on one side or the other. This determined how we viewed the world and where many of us would go on to live. South Africa was two countries—a first world country for whites

with a high standard of living, excellent education and health-care systems, and an easy life style made possible by the exploitation of the cheap labor. Blacks, East Asians, and mixed-race citizens made up the third world section of the country often amid squalid poverty. The police, and later the military, maintained a totalitarian, racist state, marked by absence of human rights.

I attended King Edward VII High, one of South Africa oldest schools, founded in 1902. It was modeled on the great private English high schools but in fact was a public government school. I received an excellent education in both the liberal arts and the sciences, together with outstanding sporting, drama, music, and debating facilities. My education was well-rounded and has always remained with me. The environment was strict, monitored both physically and nonphysically, with little emphasis on developing personal initiative. Black students were not permitted to attend white schools but after Mandela and the ANC assumed power, I was thrilled to see how this had changed.

I finished high school in 1960 and was awarded an American Field Service (AFS) scholarship to spend a senior year in an American high school. I was placed in Huntington Beach, California with a wonderful family who have become almost as close to me as my own. For a young man from all-boys King Edward VII, it was a wonderful year (enhanced by taking classes with girls with California tans). I also was allowed to choose subjects, encouraged to write essays of my own thoughts, and to take part in free discussions in class with some outstanding teachers. I was expected to take part in all the student activities, but also to go out into the community to give talks to many groups, such as the Rotarians, the PTAs, and, being Orange County, some very conservative Daughters of the American Revolution (DAR)-type groups. At that time, I was too naive to discern that racism and bigotry were also part of the society but the atmosphere engendered by the new, young President Kennedy and the generally liberal society convinced me that I would leave South Africa one day. Intense encounters in the region with other AFS students from countries all over the world stimulated my life-long involvement in larger national and international communities.

MEDICAL SCHOOL AND BEYOND

At the age of 17, with much trepidation, I entered Witwatersrand University Medical School in Johannesburg. I had not wished to do medicine; in school, my favorite subjects had been in the humanities. However, it was a time when there was strong pressure to do something practical, especially from immigrant parents, and following one's heart was not really a viable option.

The curriculum had premed and basic medical subjects for three years, followed by three years of intense clinical training. The training was excellent, if you were white. The few nonwhites who were admitted to the school were not allowed into the segregated white hospitals for their clinical rotations and could not even observe autopsies on white patients. (They were allowed afterwards to look at the organs.) To this day, I shudder when I think of their daily humiliation, while I was so unjustly favored. The background in anatomy,

pathology and physiology, often learned by rote, was excellent, although traditional, hierarchical and rigid; the clinical education in the wards, however, was wonderful. Our clinical teachers were outstanding and dedicated. We spent hours daily on small group teaching rounds under great supervision. We rotated through the large public hospitals, with a quantity and variety of clinical material that attracted medical students and residents from all over the world.

Years later, I used the same small group methods for teaching at Queen's University in neuropathology, and when I was given a teaching excellence award, I was amused by students' comments that while my lectures were good, they particularly liked the "new curriculum" small group teaching. Little did they know these methods were probably at least half a century old.

My internship in internal medicine and surgery furthered my excellent, although again rigid, clinical training and stood me in great stead throughout my career in tackling clinicopathologic problems. My interest in pathology grew as I started to wonder about the genesis of the phenomena I was observing in the wards. I enjoyed clinical medicine and have always missed it; however, I began to believe that pathology offered me a better mix of basic and clinical research and practice. (This was not an accurate observation, i.e. fine basic research has been carried out by so many of my colleagues who treat patients directly, many of whom have been my collaborators). I was lucky enough to be accepted for a residency in pathology at Stanford University Medical School.

First, however, I had to do my compulsory year in the army that had been deferred until I finished medical school. With many from my class, I did three months of basic training, which most of us completed with little enthusiasm, interest or success; we were then farmed out to the various army hospitals and clinics around the country, luckily before there was significant military activity in Southern Africa. The days were filled with army routine, protocol, and boredom, but I did see some different parts of the country, and together with my friends, we enjoyed some Hawkeye and BJ moments. I then spent six months doing epidemiological research on scleroderma in silicotic mine workers, (which turned out to be more interesting than I had expected), before my wife Vivien and I left for our new life in North America. When I look back on growing up in South Africa, I realize how much it shaped me. All aspects of the country, from its apartheid horrors to its beauty, its landscapes, seascapes and wildlife, to my education, family, and friends, have influenced my professional, personal and socio-political views ever since.

THE STANFORD YEARS

The Stanford Department of Pathology was a very exciting place in 1970 (Fig. 2). The Chair, David Korn, was young, (trained at Harvard and the NIH), ambitious and enthusiastic. Besides having a commitment to morphological pathology, he represented the new breed of molecular pathologist. He quickly staffed a previously quiet Department with outstanding faculty. Ron Dorfman and Dick Kempson from Washington University ran the surgical pathology side; they attracted excellent faculty and created a wonderful, busy academic divi-

sion. Ron acted in "Loco God-Parentis" to my two sons who were born at Stanford. The autopsy service was run separately, also by some fine pathologists. David also hired some outstanding basic and clinical researchers, including Irv Weissman, one of the world's preeminent immunologists, David Clayton and Errol Friedberg, two molecular biologists, and Klaus Bensch, an experimental pathologist from Yale. All these people combined to make the perfect balance of service and research, and Stanford itself provided a wonderful scientific and clinical milieu, with Joshua Lederberg and Arthur Kornberg, two Nobelists, on staff. Almost by osmosis, I learned a great deal of immunology and molecular biology, without ever having taken any formal courses.

David was instrumental in starting my research career. Within a few weeks of my arrival, he called me into his office, and told me: (i) that I should become a researcher as well as a diagnostic pathologist, (ii) that I should do this with Klaus Bensch, and (iii) that they had already chosen my project. Being a good British-type trained student, I said "Yes-sir", and together with Klaus and a pediatrician, Bill Northway, I studied oxygen toxicity in newborn mice over the next couple of years, which yielded some nice papers. David watched over my career for a long time. He later became Dean at Stanford, then left for the Association of American Medical Colleges (AAMC) in Washington, and finally returned to Harvard. We have reconnected at times, and I am forever grateful to him, and all these other wonderful teachers.

While the training in anatomic pathology was great, it was also mainly enjoyable. I worked and socialized with some excellent fellow residents, including Roger Warnke and Michael Hendrickson, who, respectively, took over from Ron Dorfman and Dick Kempson, Richard Sibley, Peter Windhorst, and Chuck Zaloudek. In addition, Paul Manley a Canadian who became a GI pathologist, and who has been a lifelong close friend, returned to Ontario, and played a large part in my later move to Queen's.

THE START OF NEUROPATHOLOGY

I had always loved neurology and had toyed with the idea of specializing in it. Soon after starting my neuropathology rotation, I realized that I had found the right mate. My passion was also stoked by the incomparable Lucien Rubinstein. He was Belgian but was trained in Britain by Dorothy Russell; and he was one of the world's eminent experts in CNS neoplasia; he also had a great understanding of all of neuropathology. Lesions seemed to talk to him, and yield their diagnoses. (This did not include muscle pathology, which he obviously disliked). A true Renaissance man of enormous intellect, with a classical European background in languages, music, literature and art, he was tall and elegant, a dominant and domineering figure with a unique style and flair. He was a great teacher and a superb lecturer; his trainees benefited greatly from the large number of cases sent to him for consultation from around the world. His weekly reviews of these cases with the fellows were marvelous. A complete perfectionist, he would revise and rerevise our papers and conference presentations with us until they met his standards (or until we were ready to kill him). We shared a common love of opera, and our sign-out



FIGURE 2. Stanford. Top: David Korn, Lucien Rubinstein, and Ron Dorfman. Bottom: Larry Eng, Lysia Forno, and Richard Kempson.

sessions always included a hot discussion of the previous week's San Francisco performance; I would always learn something from him.

Two other people also were vitally important in my training at Stanford. Lysia Forno, a Dane trained also in neurology and neurosurgery, was the neuropathologist at the VA hospital, through which we all rotated. Small, shy and diffident she was the opposite of Lucien. However, her knowledge of nonneoplastic disease was encyclopedic, and was coupled to an outstanding morphological eye and a razor-sharp intellect. Internationally respected for her studies on Parkinson disease, she filled in all the gaps in our nonneoplastic experience, and taught us the essential value of clinicopathological correlation. Beloved by all her trainees, Lucien respected her highly, and frequently deferred to her opinion. She received the AANP Meritorious Service Award, and I was honored to have introduced her career at the ceremony. Ray Sobel, an outstanding MS research pathologist, who later headed the AANP and the *Journal* and was lured from Harvard to the VA, also was a fan, and worked very closely with her.

The other was Larry Eng, a great neurochemist, who first isolated and characterized glial fibrillary acidic protein (GFAP), at a time when brain-specific proteins were being dis-

covered and functionally investigated. Under him, I learned new research methods, and did some of the first immunoperoxidase staining of GFAP distribution in the normal brain, and in experimental and clinical tumors. This longstanding interest in astrocyte function continues. Through Larry I met Marion Smith and Fritz Seil who were working on models of multiple sclerosis, and Steve Waxman, (later to Yale), and I was hooked.

Some excellent fellow neuropathology trainees and friends with whom I worked included Don Rawlinson (to Cornell), a good friend who died tragically young, and Alex Spence who went to the University of Washington. Steve DeArmond followed me in Larry's lab and had a wonderful career in San Francisco helping Stan Prusiner win the Nobel prize for his work on prions. Bernd Scheithauer, (at The Mayo Clinic), and Scott Vandenberg (at UC San Francisco), followed Lucien into the oncology field with great success. Bernd and I taught CNS surgical pathology courses for some years at USCAP; he remained a good friend until his untimely death. Frances Conley, who became the first academic female neurosurgeon in the USA, was a fellow trainee. She was strong enough to put Lucien in his place, and he adored her for it.



FIGURE 3. Queen's. Top: Nathan Kaufman and David Robertson. Bottom: Henry and June Dinsdale, John Marshall, and Sukriti Nag.

LIFE AS A GROWN-UP

In 1975, I finally followed my father-in-law's entreaties to grow up and get a real job, which I found at Queen's University, one of Canada's oldest, in Kingston, Ontario. Kingston is a beautiful small historic city, Canada's first capital, in the Thousand Islands where Lake Ontario flows into the St. Lawrence River. It had an ease of living, and cultural and outdoor facilities that made for a wonderful quality of life. As a big-city boy, I originally was certain that I would remain there no more than five years. Well, it has now been 43 years.

Nathan Kaufman, the Head of the Department, and David Robertson, who ran the Division of Neuropathology, recruited me from Stanford (Fig. 3). Both were well known. Nathan was a wonderful Head, who had come back to Canada from Duke. An iron metabolism researcher, he was President of the IAP and editor of *Laboratory Investigation*. David, the Director of neuropathology, had trained at Duke with Steve Vogel, and at Queen Square in London. Lucien knew David, and after being satisfied that "his boy" would be well treated, gave his blessing. My old friend and fellow resident at Stanford, Paul Manley, also played a large role in my move, not in the least because his wife Katherine persuaded Vivien that this was the place in which she would be happy. Nathan had built up a very fine academic department, with high standards of service and teaching. He also recruited researchers both basic and translational, and set up a fine cancer group, which would one day grow into a power-house. He watched over my career, both before and long after he retired from Queen's and we remained close and good friends until his death last year at age 100.

David, who took over as Department Head, was about as good a pathologist as I have ever known. A superb diagnostician and teacher, he also set up a fine program in CNS vascular research, together with Henry Dinsdale, the head of neurology. Sukriti Nag, one of David's research trainees, has since become an expert on the blood-brain barrier in her own right. David also seemed to pull the whole clinical group together. His brain-cutting sessions were wonderful; trainees in neuropathology, pathology, neurology and neurosurgery attended these faithfully, as well as most of the faculty in these disciplines. Neuropathology therefore had real stature at Queen's. David, Henry and John Marshall, the head of neurosurgery, set a standard for quality collegial cooperation. David also protected me in the early years from anything that would have interfered with my service, teaching and research, but found many opportunities to advance my career; he and his wife Alice were good friends of ours. I also received considerable assistance from members of the basic science departments who right from the beginning generously opened their store-rooms to help me equip my lab.

I split the neuropathology service and teaching with David, and then when I became Director of Neuropathology, with John Rossiter, in addition to doing my research. I loved the neuro cases—each autopsy and surgical presented me with a fresh challenge, and I confess to a slight thrill each time I picked up the first slide. I got enormous pleasure watching the residents develop their "eyes" and analytic skills. I also rotated on the general autopsy service, enjoyed the hospital cases, but hated medicolegals. I taught residents, medical and undergraduate bioscience students in lectures, seminars and small groups. Towards the end of my career, the increasing emphasis on objective-based teaching, and the antipathy of many students to information not within these stated objectives, diminished some of my enthusiasm.

A succession of excellent Heads supported my career after Nathan and David; these were Bob Kisilevsky, Paul Manley, and Iain Young, and for a shorter time, Victor Tron. All of them deserve my heartfelt thanks.

We had wonderful trainees in neuropathology, as well as those from neurology, ophthalmology, and pathology, many of who rotated for a full year with us. Most of the neuropathology residents have gone on to excellent careers in academia, and I am delighted that they have remained close friends (Fig. 4). Wayne Moore, is now a well-established MS researcher. Ed Johnson who was head of neuropathology in the University of Alberta, and David Munoz at the University of Toronto, a leading expert on degenerative CNS diseases, (who did me the honor of naming his son after me), both did a lot of research with me. David Ramsay, at the University of Western Ontario (UWO), is a well-published forensic expert. Finally, John Rossiter, one of our trainees, then joined the department as a faculty member. An outstanding diagnostician, teacher and colleague, he took over my position as director of neuropathology. I cannot thank enough my two wonderful technicians, first Lloyd Kennedy and then Mirta Chiong, without whom I would never have been able to do my research, and I am also so grateful for the remarkable secretarial and administrative assistance and mollycoddling I received from Pat Scilley, Kevin Kell, and Linda Oster. All in all, my years at



FIGURE 4. Neuropathology residents. Top: Edward S. Johnson and David Munoz. Bottom: Wayne Moore and John Rossiter.

Queen's were very pleasurable and gratifying, and allowed me to flourish and spread my wings widely.

Queen's had a small patient base and although there were some outstanding research neuroscientists, they were mostly interested in the physiology of neurons and in neuropharmacology. There were almost no researchers in MS and its related biology. Collaboration outside the institution became vital for my career. Therefore, in the early 1990's, I went to the UWO, as Head of Pathology, in London, Ontario. This was a very fine job in an excellent institution, with a strong and varied neurosciences presence, including MS. Unfortunately, we could not find a job there for my wife, who was the Head of the Health Sciences Library at Queen's, and after almost two years of commuting about every second weekend, we decided that life was too short, and I moved back to Queen's where I worked until official retirement in 2010.

Like others, I picked up extensive administrative duties in the medical school, serving on many committees, culminating in a five-year term as Associate Dean, heading the research portfolio. I also served on many committees of the Canadian Institute for Medical Research and its predecessor, the MRC, and the Royal College of Physicians of Canada. The same process occurred in the hospital, where I spent a term as Medical Director, and then became the Vice-President Research.

I retired from the Department as an Emeritus Professor in 2010, and was invited to join McGill University's famed Montreal Neurological Institute (MNI) as a Visiting Scientist. The MNI has a very strong MS program, and I now continue my previous collaborations with my friends and colleagues there on a part-time basis. I do only research, and the

interaction with some wonderful faculty, postdoctoral fellows and graduate students, is a great experience. In addition, I love visiting Montreal for its great cultural activities and the food is outstanding. My good friend and colleague, Jack Antel, one of the world's eminent MS figures and his whole group, have made this a most rewarding experience. Sadly (for me), Amit Bar-Or was lured to Pennsylvania, and I miss his wisdom and expertise.

SABBATICAL

In September 1999, I took my first Sabbatical, and spent one of the happiest years of my professional life. I first joined my good friend Hans Lassmann in Vienna, and spent a couple of weeks looking at his vast collection of cases, especially those from the Mayo Clinic on which he and Claudia Lucchinetti were to base their famous, if somewhat controversial, pathogenetic classification of MS lesions. We then travelled to Cambridge University, where my longstanding colleagues, Bill Blakemore and Robin Franklin, who was his student and is now a star researcher in his own right, hosted us graciously. We spent the days looking at and discussing different models, research methods and directions. We then traveled to Washington DC, where we stayed until August 2000. I had a visiting fellowship position at the NIH, in the neuro-immunology branch headed by Henry McFarland, who had founded it with the late Dale McFarlin. Many eminent figures in the field of MS, including Mike Racke and Amy Lovett-Racke, Cedric Raine, Steve Jacobson, Anne Cross, Rhonda Voskuhl, and Roland Martin had spent time there. The tradition continued with the training of today's crop of stars, including Ben Segal, Daniel Reich and Peter Calabresi. I squatted in Steve's lab, and developed a great relationship with him. I had originally planned to do some imaging correlates of elements of the demyelinating process in piglets, but, "the best-laid plans of mice and men. . . ." Despite prior careful study of the pig brain, we found at surgery that the pig lacks a significant falx, and we caused massive hemorrhage as the meninges were fused. However, there were plenty of other things on which to work.

All were amazingly welcoming and generous to me. I also rediscovered the joys of sitting in a library but the glue and high standards that created this atmosphere came from Henry. He was an outstanding clinician, and his knowledge of immunology was wonderful as expected; I was not prepared for his deep understanding of imaging, or for his understanding about what made sense in the pathology. He instantly could grasp the most complex problems. It was a magical and rejuvenating year, and I am forever grateful for the opportunity.

REACHING TO THE OUTSIDE WORLD

I have spent much of my general neuropathology career in three "homes", the Canadian and American Associations of Neuropathology (CANP and AANP), and later the International Society of Neuropathology (ISN).



FIGURE 5. AANP colleagues: Top: Mike Hart, Asao Hirano, Harry Webster, and Bernd Scheithauer. Bottom: Steve DeArmond, James Powers, Clayton Wiley, and Moses Rodriguez.

THE CANP

I joined the CANP soon after arriving at Queen's. It was a small organization, which together with the Royal College helped establish the very high standards for training in Canada; these were copied by many other jurisdictions around the world. There was an excellent annual meeting, mainly clinical, informal and inclusive, which also attracted neuropathologists from the States, some of whom had trained in Canada. The founding generation, Morris Finlayson and Sterling Carpenter (McGill), Barry Rewcastle (Toronto, later Calgary), David Robertson (Queen's), Lorrie Dolman and Margaret Norman (Vancouver), and John Kaufman (UWO), were supportive and welcoming colleagues. As at Queen's, they all trained very successful residents and fellows. As my generation aged, we took over many of the responsibilities, and both Joe Gilbert (UWO) and I became Presidents of the Association. Larry Becker, sadly deceased, and Dawna Armstrong headed an outstanding pediatric neuropathology unit at the Hospital for Sick Children, and were joined in Toronto by Sukriti Nag and Bill Halliday. Ken Berry and Katerina Dorovini-Zis joined Lorry Dolman in Vancouver. Joe, Larry and I also organized a very successful International

Congress in Toronto, which whitened our hair, but left the Association with a lot of prestige and a large amount of money. The organization has grown, thrived and is now run by the generation of our trainees. Marc del Bigio, Ian MacKenzie, David Munoz, and Rob Hammond, are only some of the many outstanding younger neuropathologists. Most members are also members of the AANP.

THE AANP

The AANP has been my other home. When I joined, it comprised a collection of giants in the field: Lucien, Bob Terry, Nick Gonatas, John Kepes, Lucy Rorke, Igor Klatzo, and Ken Earle, to name only a few, who ran it, often in an intense and at times humorous way. Our generation contains far fewer real characters. Numerous experimental neurologists and neuroscientists also found a home there, although, sadly, less so now.

My research career was considerably improved by interaction with more experienced myelin gurus such as Asao Hirano, Murray Bornstein, Buster Alvord, Harry Webster, Peter Lampert, Cedric Raine, Henry Wisniewski, and Pat Cancilla (Fig. 5). They opened their arms, labs and thoughts to me, and gave me guidance and critical assessments, always with a



FIGURE 6. The ISN. Top: Hume Adams, Georg Kreutzberg, and I. Bottom: Paul Kleihues (left), the Scandinavians (right), Patrick Sourander Yngve Olsson, and Hannu Kalimo.

generosity that surprised me. I hope I have learned to behave accordingly. There were so many accomplished peers, among them Ray Sobel in MS, as well as Tessa Hedley-White, Richard Davis, Joe Parisi, Bette DeMasters, Barbara Crain, Harry Vinters, John Trojanowski, and Dino Ghetti, in other fields. Of course, I cannot name all, but the irrepressible and highly talented Jim Powers (with whom I visited Machu Picchu, who I meet for postretirement lunches midway in Syracuse and who has led me astray in the evenings at many meetings), Mike Hart and Clayton Wiley, both outstanding researchers and leaders, are among those with whom I continue to share friendship (Fig. 6). The AANP also was enhanced with the membership of great researchers from all over the world, including Kurt Jellinger, Hans Lassmann, Franz Seitelberger, Seth Love, and Roy Weller. It has also been a pleasure to see the organization now run by the next generation of stars, including David Louis, Jeff Golden, and Arie Perry to name a few.

I was very grateful to have been chosen as the Saul Korey Lecturer, and then in 2010, awarded the Association's Meritorious Service award, which I shared that year with my old friend and fellow resident, Steve DeArmond. We both thanked many of the same people.

THE ISN

In the 1980s I became the Canadian representative to the ISN, and this organization became a large part of my life until 2006. I became Secretary General and served under three outstanding Presidents and excellent investigative neuropathologists, Hume Adams (Scotland), Georg Kreutzberg (Germany), and Harry Webster (USA) (Fig. 6). I developed strong relationships with them, visited them, and learned a great deal, all of which came in very useful when I became President. The organization mainly ran excellent International Congresses, but during Harry's tenure, Paul Kleihues, (Germany and Switzerland) single-handedly, with our help and encouragement, started *Brain Pathology*, at first producing it with his wife in his home. Its success has been assured. An expert neurooncologist, Paul later became head of the IARC division of the WHO. We also developed the book series, *Pathology and Genetics* in collaboration with the WHO. Yngve Olsson (Sweden) was the overall editor and many have since been produced. The ISN and its congresses have enabled me to travel extensively and I still marvel at the number of wonderful people I have met and learned from, not only about neuropathology. A highlight of my tenure as Secretary, was a

month-long working trip of about 30 neuropathologists to China in the early 1990s, organized by the ISN and led by Harry, Yngve, and me. Another highlight came from the Italian Society, which ran the 2013 Congress when I was the President. I had helped them with the organization, and Davide Schiffer rewarded me with a trip to the Holy of Holies, a day at the Ferrari factory and the racing test track. As my wife said, (somewhat sarcastically), even Presidents don't grow up. Françoise Gray (France) took over from me as president with great success. My memories of these connections are priceless.

MY YEARS SEARCHING FOR THE MEANING OF LIFE (WELL, BRAIN FUNCTION)

During residency, I accumulated some research papers on astrocytes with Larry Eng, on lungs with Klaus Bensch, and a few papers on tumors, both experimental and clinical. Our paper delineating the papillary meningioma was one of my favorites, mainly because Lucien included Dorothy Russell, who had been his mentor and coauthor of Russell and Rubinstein's classic text. As a resident, I was thrilled that the author list read Ludwin, Russell, and Rubinstein. At Queen's, I retained a clinical fondness for neuro-oncology, and wrote a few papers as the reviewing pathologist on the trials of the National Cancer Institute in Canada. I also had publications on congenital malformations, Pick disease and other degenerative diseases. I collaborated with the neuropharmacologists on the pathology of neurotransmitter toxicity. However, I was already committed to the investigation of multiple sclerosis. This cruel disease of the young, with a fuzzy etiology, and a strong smell of neuro-immunology, which had piqued my interest at Stanford, has kept me fascinated, puzzled and motivated ever since.

LIFE IN MS

I started my MS-related work in 1976, studying experimental demyelination and remyelination. I mainly used the cuprizone model pioneered by Bill Blakemore, who was most helpful in getting me on track. In those days, many were skeptical that brain repair was possible. Bill, and then I, showed this to be true, by causing pure demyelination following oligodendrocyte necrosis, in predictable areas at predictable times, and then watching remyelination occur in a similar fashion. There has been a surge of interest in this model of late. Remyelination, recognized by thin myelin sheaths, has also been shown following demyelination by lysolecithin or ethidium bromide administration, and following the induction of experimental allergic encephalomyelitis. These morphological features have been used as a marker of remyelination in MS. I was interested in the generation of remyelinating oligodendrocytes, and investigated this with proliferation experiments. We showed that these arose from immature oligodendrocytes in the demyelination phase, with maturation and remyelination in the recovery stage. We also described in these experiments, the proliferation of mature astrocytes, questioned for a long time, but recently verified. Keeping the animals chronically demyelinated, or subject to repeated insults, reduced remyelination when taken off the drug. I was fortunate to be honored

with the Weil Award in Experimental Neuropathology for these studies. Bill had already shown that aged animals remyelinated less than young ones. Ludwig and Nancy Sternberger taught me the elements of EM immunocytochemistry, which I used to define the progression of myelin proteins during remyelination. In other experiments, we showed that while oligodendrocytes from implanted normal CNS migrated freely through the tissue, those entrapped in astro-glial tissue caused by chronic Wallerian degeneration in the optic nerve, while retaining their myelination properties, were far more limited in their migration. This is of potential relevance for gliotic MS plaques. These observations on astrocyte function remained on my mind for many years and I have very recently returned to tackle the problems.

Another early observation has persisted for years. With Ed Johnson, I described the "dying-back" gliopathy, where we showed that in chronic cuprizone toxicity, the distal processes of the oligodendrocyte degenerated before changes in the perikaryon, and led to demyelination. We also saw this in Mario Moscarello's (Toronto) DM20 mutant model. Moses Rodriguez then demonstrated the same changes in MS biopsies, and Claudia Lucchinetti and Hans Lassmann used it to define their type III pattern of MS. The possibility that this was caused by shutting down a luxury function in a severely stressed but still viable cell occurred to us, but we did not have the facilities to test this. Years later at the MNI, we have returned to this problem. In addition, I have helped Veronica Miron and Jack Antel at the MNI, to study the demyelinating agents described above *in vivo* and *in vitro*, and to test the enhancement of remyelination by disease-modulating agents; others are using the myelination of synthetic fibers for the same purpose.

Early on I showed that the perineuronal satellite oligodendrocyte, previously of questionable functional relevance, played a role in remyelination. I collaborated with Sara Suzchet (Chicago), using her sheep oligodendrocytes to myelinate rat dorsal ganglion neurons, and showed that in contrast to rat oligodendrocytes where the myelin compacted, these cells contacted and wrapped the axons but did not complete compaction, suggesting different signals for these processes. With Mario Moscarello (Toronto), we described the process of demyelination and remyelination in transgenic DM20 mutant mice, and their amelioration with taxol. I also worked with Mario and John Whitaker, to show that this agent inhibited EAE. On sabbatical at the NIH, I collaborated with multiple researchers in the Neuroimmunology branch. With Steve Jacobson and Claudio Cermelli, we showed Herpes virus 6 in MS tissue, while with Roland Martin and Bill Biddison, microarrays showed the differences in gene expression between acute and chronic disease, and a new player, lipooxygenase. I helped Koichi Ito and Roland to demonstrate the pathology and pathogenic potential of MS patient T cells in EAE induction, and I assisted on the pathology of EAE in the marmoset with Joe Frank.

Over the years, I have written many reviews and chapters on MS pathology, and on the subjects above. I have collaborated on some interesting work on the pathogenesis of Balò's Concentric Sclerosis with Christina Stadelmann and Hans Lassmann, and on various staging and classifications of the disease. The latest of these, with Tanja Kuhlmann



FIGURE 7. Some of my MS Research Colleagues: Top: Jack Antel, Hans Lassmann, and Henry McFarland. Bottom: Cedric Raine, Amit Bar-Or, and Wee Yong.

(Münster), Jack Antel (MNI), Wolfgang Bruck (Göttingen), and Hans Lassmann has only recently been published. I have assisted Amit Bar-Or's (formerly MNI, now U. of Pennsylvania), and Jen Gommerman's (Toronto) groups in looking at the role played by meningeal inflammation in causing cortical pathology in MS (Fig. 7).

Since I started regularly at the MNI, there have been some wonderful opportunities to return to some of the incompletely answered questions of my earlier life. Jack and his group were also interested in sublethal damage to oligodendrocytes, and we showed in culture that stressed oligos retracted their processes, and then regrew them when distressed. The mechanisms are very similar to the dying-back feature in vivo, and the clinical implications are obvious. We are currently testing this further in culture, as well as reviewing with Moses Rodriguez the old MS electron microscopic images, to redefine these changes. In these experiments, we are collaborating with Tim Kennedy, a wonderful neurobiologist, who is very interested in oligodendrocyte cellular transport. I have also returned to my very first love, the

astrocyte, and have, with an excellent postdoc at the MNI, Vijay Rao, carried out single cell laser capture microRNA studies of astrocytes in health and disease. First, we demonstrated the topographical variations in astrocyte function in normal adult and fetal human tissue. We are now studying the variations in these functions in various areas and differing stages of diseases, including MS. I find it fascinating to see how science often operates in circles of discovery and rediscovery. I am also so grateful for the collaborative support I have received from all these people, and can only hope that I have also helped them. I am also delighted to still be participating in the unlocking of the pathogenesis of this disease.

OFF-SHOOTS FROM MY RESEARCH

I spent 35 years with the Multiple Sclerosis Society of Canada, a wonderful organization, dedicated to both patient care and research. Allister Fraser, Yves Savoie, Bill McIlroy, Deanna Groetzing and Sandy Aird were wonderful administrators and pushed the program (and me) along beautifully. I occupied many positions, including chairing the Medical



FIGURE 8. The Myelin Project: Top: Augusto Odone, Monique Dubois-Dalcq and David Colman, Annik Baron-von Evercooren. Bottom: Bill Blakemore and Catherine Lubetzki, Ian Duncan, Susan Sarandon and me, Robin Franklin.

Advisory Committee, and serving on the National Board of Directors. This brought me in touch with almost all the great MS researchers in Canada at the time, including pioneering figures such as Don Paty, Jock Murray, George Ebers, Dessa Sadovnik, Jack Antel, Wee Yong, Mark Freedman, Amit Bar-Or, and Brenda Banwell, to name just a few. The baton has been passed to a whole new crop of MS specialists. I also spent much time lecturing and talking to patient groups, and marveled at the spirit, resilience and sophistication of these remarkable people and their families, who faced such huge burdens. One of my most satisfying achievements was to be part of creating the society's endMS National Research Training Network. I toured the country helping raise the \$20 million required, and drumming up support among researchers. We created a unique community of a new generation of investigators, linked across the country through conferences, regional programs, summer schools and advanced research program training. It was and still remains a great success. It was a great honor to be awarded the Queen Elizabeth II Golden Jubilee Medal for services to MS in Canada.

Another very satisfying and unique experience was my participation for almost 20 years in the Myelin Project. This was founded by Augusto and Michaela Odone, whose son, Lorenzo, developed adrenoleukodystrophy. Augusto, an Italian-American banker with the World Bank, carried out his own research and devised a compound, erucic acid, which

successfully brought down the high long-chain free fatty acid level in the blood of these patients (The cause of the disease was later to be attributed to a peroxisomal disorder, and the clinical effects were marginal). However, he then started to tackle remyelination, to correct the damage already done. At that time remyelination was not nearly as well-accepted, and popularly studied a phenomenon as it is now. He called it his Manhattan Project. He raised money for research internationally, and attracted some of the best-known figures in the field, including Bill Blakemore, one of the real pioneers, Ian Duncan, David Colman, Monique Dubois-Dalcq, Annik Baron-von Evercooren, Caterina Lubetzki, and Boris Zalc (Fig. 8). Later additions were Robin Franklin, Charles ffrench-Constant and Gian-Vito Martino as well as others. The roots of the organization were depicted in the Oscar Nominated movie, "Lorenzo's Oil". I think the only time my children were impressed with my scientific career was when I was photographed with Susan Sarandon at the movie's premiere. The meetings were terrific, I learned a lot, and the scientific output has been highly successful; the clinical translation has, however, been slow. Augusto, with whom I was very close, came to recognize that science goes at its own pace, that Lorenzo would probably not be cured, but that basic research has to go forward. They both died in the last few years.

I was also on the Scientific Advisory Board of a similar organization, The Myelin Repair Foundation, out of San Francisco. Started by Scott Johnson, a successful



FIGURE 9. Passages. Top: From the wilds of Africa (left) to the beauty of the St. Lawrence River from my bedroom (right). Middle and Bottom: The bucket list (version 1): Everest, Taj Mahal, Great Wall with Bud Dudley, and Machu Picchu.



FIGURE 10. Family: Top: Stacey, Derek, Raymond, and Karen. Bottom: Andrew, Self, Vivien, and Elizabeth.

businessman with MS, the money raised supported some outstanding research for a while, but translation was slow, and it eventually faded. These two projects were testaments to what could be achieved by committed nonprofessional individuals.

ECTRIMS AND ACTRIMS

These two organizations, the European/Americas Committee for Treatment and Research in Multiple Sclerosis, have become the go-to sources for learning and disseminating research in MS. ECTRIMS, the larger, holds an annual meeting, and multiple individual and regional educational opportunities. ACTRIMS also has a very successful annual meeting, and is establishing itself as the voice of academic MS study in North America. They hold a combined meeting every three years, and this year's meeting was terrific and attracted 11,000 attendees. I have served on ECTRIMS committees and the ACTRIMS Board, and have taught and presented at both venues. They showcase genetics, environmental factors, epidemiology, imaging, pathology, immunology, neurology, rehabilitation and nursing, and are highly multidisciplinary. Given the high profile of pathology and neuropathologists in MS circles, for many, sadly, these meetings are more relevant than our traditional pathology gatherings. I guess one follows the money and where people show interest.

THE ETHICS EXPERIENCE

Many years ago, a few of us started a regular series of discussions in medical ethics in the hospital. I was then ordered (literally) by the Dean to teach "this ethics stuff" to second year students, which I somehow managed to do, mainly by reading up the night before the lectures. It went surprisingly well, until I finally informed the Dean that in life you get what you pay for and as I wasn't being paid, I thought the students deserved better. Very grudgingly he appointed a real ethicist. I remained involved in the subject and finally spent about six years serving on, and then chairing, the Canadian Federal Human Research Ethics Panel, responsible for formulating national research ethics regulations and guidelines across the whole spectrum of research in Biomedicine, Humanities and Science. Again, the opportunity to learn from ethicists, philosophers, lawyers, psychologists and business professors on the Panel has been one of the most rewarding aspects of my career.

LIFE OUTSIDE NEUROPATHOLOGY

Working only part time, I now spend a lot more time with my family and friends. I have taken up the piano again quite seriously, with the help of an extremely tolerant and patient teacher. Kingston has a very active musical scene, and I am on the Board of the Kingston Symphony. I am also

president of a charitable foundation funding educational projects supporting and retaining students in difficulty. I belong to some multidisciplinary discussion groups. Over the years I have been an antique map collector, a (very mediocre) golfer, an enthusiastic if not overly successful Masters swimmer, hiker and windsurfer, and a mountain climbing groupie. I continue to love traveling, and have satisfied my original bucket list, Everest, Machu Pichu, the Taj Mahal, and the Great Wall of China. (The latter three were helped by associated work trips—for some strange reason, the neuropath opportunities around Everest were hard to find). I am now compiling version two of the list, although find that the actual getting there is increasingly less pleasant. Age has impinged on many of these activities (Fig. 9).

FAMILY: MY LOVES AND ANCHORS

I met Vivien in my last year at medical school. She was a French major, who became a teacher and then a librarian.

We married after internship, 49 years ago. At Queen's she became the Head of the Faculty of Health Sciences library and a pioneer in information literacy; she was one of the first to incorporate this formally into the medical school curriculum. She is now happily retired, heavily involved in charities supporting orphaned AIDS children in Lesotho and First Nations in Ontario, in book clubs, and seeing a lot more of her friends. Our two boys were born at Stanford. Our eldest, Derek, is now an antitrust lawyer in Washington, DC, married to Stacey a privacy lawyer. They have two children, Andrew and Elizabeth, and we wish they lived nearer to us. Our other son, Raymond, is a strategic planner and marketer in Toronto, and his partner, Karen, is a health and social services consultant to NGOs, First Nations bands and government departments. We are fortunate that they live closer. Without them my life would never have been complete, and my career would have been far less meaningful (Fig. 10).