From neurology to neuropathology and back

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Chemistry or medicine 1958-1963?

In the fifties, high school students in Germany had to select their career goals without much guidance or college education. I was a student at a gymnasium of mathematics and natural sciences in Osterode, a provincial town near the Harz Mountains in Lower Saxony of Germany. My father, a general practitioner in a small town in the Harz, had different ideas. He wanted me to be a medical student and ultimately take over his practice. The university town, Göttingen, was located 50 km from our home. Göttingen was then a small town, but medical education was excellent and diverse. I stayed in a room near the Max Planck Institute where Otto Hahn, the Nobel laureate in nuclear fission, was still active. My inaugural dissertation involved measurements of nuclear sizes in rat liver, adrenals, and endometrium after the animals were treated with drugs affecting the autonomic nervous system (Koeppen, 1963). My interest in the neurosciences began during my last year of medical school. The inaugural dissertation received the annual faculty award in 1963; and the sum of 800 Deutschmarks was sufficient to defray my cost of a trip by ocean liner to the United States where a non-profit organization, the Ventnor Foundation, had offered me a position as a medical assistant (intern) at a New Jersey hospital. After an internship of 18 months, I joined the neurology training program at Montefiore Hospital and Medical Center in New York City in 1965. Neurology education was disappointing, but I met the late Drs. Harry Zimmerman, Robert Terry, and Asao Hirano who stimulated my interest in neuropathology and, above all, clinoanatomic correlation in neurology and neurosurgery. After one year at Montefiore, I was recruited to the Department of Neurology and Psychiatry of Northwestern University School of Medicine in Chicago. My first assignment was to the Veterans Affairs (VA) Medical Center in Hines, Illinois, where the late Dr. Kevin D. Barron was the chief neurologist. Dr. Barron had been trained by Drs. Zimmerman and Terry and continued to practice neuropathology at Northwestern and the VA Medical Center. Dr. Barron was a master of clinoanatomic correlation and stressed that neurologists should have training in neuropathology. His training had a major impact on my further career as a neurologist and neuropathologist. While opposition to neurologists and psychiatrists practicing neuropathology was evolving, we were reminded of non-pathologists who had made major contributions to the practice of neuropathology. We thought of Alois Alzheimer and his 1906 illustrations of neurofibrillary tangles, and of King Engel who gave us modified trichrome in the diagnosis of mitochondrial...
myopathy. My training in neuropathology from 1969 to 1971 was enough to gain acceptance to the neuropathology board examination in 1980, and, since that time, I was convinced that I was a better neurologist because I was also a neuropathologist. During my time in Chicago, Dr. Barron insisted that I should learn neurochemistry as well, and I was assigned to the research laboratory of the late Dr. Joseph Bernsohn. Over a one-year period, I learnt standard and advanced laboratory techniques, and my initial interest in chemistry came to belated fruition. Since joining the Department of Neurology at Albany Medical College in 1969, I have maintained a neurochemical and neuropathological laboratory at the Albany VA Medical Center (figure 1) while also running the clinical neurology service. Among my valued neurochemical discoveries was a sensitive assay of brain malonyl-coenzyme A, a critical molecule in the biosynthesis of fatty acids (Mitzen and Koeppen, 1984). The autopsy practice generated access to specimens from unusual cases, such as Pelizaeus-Merzbacher disease (PMD). The neurochemical laboratory helped me identify the cause of the disease, namely, a deficiency of proteolipid protein (PLP) (Koeppen, et al., 1987). The mutation in this patient with PMD was a point mutation (Hudson, et al., 1989) though later, the mutation in most cases was identified as a duplication of the PLP gene. The PLP protein is unusual because it is soluble in a mixture of chloroform and methanol (Folch and Lees, 1951). Through the work on PMD, I met the co-discoverers of PLP, the late Dr. Marjorie B. Lees (figure 2), and the late Prof. Franz Seitelberger who had advanced the existence of a “connatal” form of PMD. Prof. Seitelberger invited me to the Neurological Institute in Vienna where I gave a lecture on PLP and PMD. Profs. Kurt Jellinger and Herbert Budka were in audience. I also discovered that the late neuropathologist, Dr. Wolfgang Zeman (figure 3), had written to Dr. Lees in 1963, proposing that PLP was a likely candidate in the genetic mutation underlying the disease. Pelizaeus-Merzbacher disease is an X-linked disorder, and Pelizaeus, a German balneologist, understood the mechanism of X-linked transmission before the existence of an X-chromosome was known. Pelizaeus (1885) stated succinctly that the “disease goes through the mother but does not do anything to her”. It is peculiar that at the time of my work on PMD, a spontaneous X-linked central nervous system myelin deficiency in rats was discovered in Albany, NY. The animal model was called “myelin-deficient (md) rat”, and the neuropathologic and genetic similarity to Pelizaeus-Merzbacher disease was remarkable (Koeppen et al, 1988). PMD patients also show a lack of other myelin proteins, and the injection of a white matter homogenate into
guinea pigs (type 13) did not cause experimental allergic encephalomyelitis (EAE). Antibodies to PLP were not commercially available, and I isolated the protein from frozen normal human white matter. Injection into rabbits caused encephalitis that closely resembled EAE. One rabbit with advanced encephalitis generated a high-titer anti-PLP antibody that worked very well on paraffin sections of human central nervous tissue. The antibody became very popular, and I forwarded samples to several foreign and domestic myelin investigators.

A new goal: the hereditary ataxias

In 1972, a patient with autosomal dominant ataxia presented with an unusual disturbance of ocular motility that became known as supranuclear pseudopseudophthalmoplegia. Many years later, the mutation was identified as a cytosine-adenine-guanine (CAG) trinucleotide repeat expansion on chromosome 12, and the disease was named spinocerebellar ataxia type 2 (SCA-2). The mutation was like the CAG trinucleotide expansions in SCA-1 and SCA-3 (Machado-Joseph disease). SCA-6, SCA-7, and SCA-17 were later also identified as the consequence of CAG trinucleotide repeat expansions. The expansions are expressed by changing the length of polyglutamine in the cognate proteins, hence, became known as polyglutamine (or polyQ) diseases. Antibodies raised against the polyQ stretch of the normal TATA-binding protein, designated “1C2”, became useful in the visualization of intranuclear inclusion bodies in the ataxic polyQ diseases and Huntington’s chorea. Stimulated by the experience with a single patient with supranuclear pseudopseudophthalmoplegia, I traveled to Scotland, his ancestral home, to search for other members of this family. Over a period of 40 days, I could not find any but discovered unrelated patients with an identical disturbance of eye movements. At that time, commercial genetic testing for SCA was not yet fully available, and the lack of saccades in some patients with ataxia became a "genetic marker" of the disease. The
discovery of supranuclear pseudoophthalmoplegia remains important but due to its variability can no longer be called a genetic marker. The Scottish experience (Koeppen et al, 1977) prompted me to apply to the Alexander-von-Humboldt Foundation for a research fellowship. The Foundation agreed, and I moved to the University of Hamburg, Germany, where I found a warm welcome in the Department of Human Genetics and the neuropathological institute of the Eppendorf University Hospital. The plan was to backtrack from autopsy records to surviving family members. The director of Eppendorf neuropathology was Prof. Hans-Joachim Colmant, a psychiatrist. He made available a huge archive of neuropathological specimens in the basement of the hospital that had survived the bombings of World War II. The chief psychiatrist during the war, Prof. Hans Bürger-Prinz, decided that the collection of slides, reaching back to 1891, should be protected against the Allied bombings and moved the collection to a secure location. Beyond specimens of ataxia, the collection also contained invaluable other cases, including Jakob's original 1920 specimens of prion disease. It was an exciting experience to study these slides and be allowed to make photographs. German neuropathologists favored Cresyl violet as their routine stain, and it was apparent that this stain does not properly show the sponginess that is readily apparent on hematoxylin-and-eosin. My stay in Hamburg was intermittent, but I benefited from the collection at the Eppendorf Hospital over an aggregate period of 2 years. On return to Albany, NY, I began to collect autopsy specimens of hereditary ataxia in a tissue repository and, to this day, make available fixed and frozen samples to other ataxia investigators.

**Another change in direction: From dominant to recessive ataxia, 1996-2021**

After Dr. Massimo Pandolfo and his group discovered the mutation in Friedreich ataxia (FA) in 1996, my interest changed, and my research now focuses on this autosomal recessive disease. Though FA is a monogenic disease, the pathology offers a fascinating array of lesions in multiple organs: brain, spinal cord, dorsal root ganglia, sensory peripheral nerves, eyes, heart, and the insulin-producing beta cells of the pancreas. Many clinicians and FA researchers consider FA a "neurodegenerative" disease, implying the existence of onset, progression, and death. The term neurodegenerative also means atrophy, and clinical onset is thought to be related to a degree of atrophy that translates to nervous system dysfunction. Neuropathologists, however, will agree that FA is also a hypoplastic disease as far as the spinal cord and dorsal root ganglia are concerned. Sectioning of the spinal cord longitudinally to represent dorsal root entry zones as Obersteiner and Redlich did in 1894 in Vienna invariably showed loss of demarcation between the peripheral nervous tissue of dorsal roots and the central nervous tissue of the spinal cord (Koeppen et al, 2017). A surprising observation in FA was the protrusion of glial tissue from the spinal cord into dorsal roots, in support of dysfunction of a local barrier called the boundary cap. This work received the 2018 Stout award from the United States and Canadian Academy of Pathology for “resolving a scientific medical problem by studying its anatomic features”. This award is my most prized recognition.

**The mystery of brain iron**

In 1967, I participated in the examination of a brain that was incrusted by hemosiderin. The diagnosis, superficial siderosis, was not difficult, but the disorder was thought to be rare, and magnetic resonance imaging with its extraordinary ability to detect brain iron, was still to come. Dr. Kevin D. Barron and I studied the specimen in detail, and I entered a 10-year period of research in normal and pathological brain iron (Koeppen et al, 1992-2002). This iron work correlated well with my later studies in FA because other researchers thought that this disease was due to iron accumulation in mitochondria of all affected organs.

**America, 1964-2021**

My fifty-seven years in the United States constitute two thirds of my life. My early youth was troubled by the experience of World War II, America has been good to me. I waved goodbye to Europe when the Maasdam, a passenger liner of the Holland-America Line put out to sea in late January 1964, and I greeted the Statue of Liberty 10 days
later. I was never homesick, but occasionally think of my time as a refugee at the end of World War II. In January 1945, my mother packed some essentials and took me, two brothers, and a sister by bus to the west, leaving the then German province of Silesia. At that time, our father was a prisoner of war in an American camp near Naples, Italy, and did not return to Germany until 1947. Things did not stabilize until 1949 when the family walked across the border between the newly established Communist German Democratic Republic and the American zone of West Germany. Food, drink, and clothing were scarce, and we spent one year in a displaced-persons camp. The privations ended in 1950 when the German economy improved with the outstanding help of the Marshall Plan. After I became more established in the United States, I raised a family and met many good people. I want to thank my teachers of neurology and neuropathology, among whom my friend and colleague for 47 years, the late Dr. Kevin D. Barron, was the most important (figure 4). The United States continues to fascinate me, and, during my Chicago years, the sky of the Midwest seemed higher and bluer. I did not forget my European origin or my years of medical education in Germany. I am still trilingual (English, German, and Spanish) and enjoy the occasional opportunity to practice three languages. I also became an amateur radio operator (a “ham” in American lingo), and my last conversation with my late father was by ham radio. While on sabbatical in Hamburg, I received the call sign of DJ0RF wherein the “DJ0” was reserved for foreign nationals who had an amateur radio license in their home countries. Ham radio will be my main pursuit after I finally retire from research or the practice of neurology and neuropathology.

A final word: Do we teach enough clinicoanatomic correlation?

We hear a lot from proponents of “evidence-based” medicine but rarely about the art of medicine. Clinicoanatomic correlation benefits from both, and thinking of brain structure while considering a differential diagnosis is a rewarding exercise. Senior physicians will agree that anatomy and pathology are the basis of medicine. Telehealth has arrived and is perhaps not in line with the art of medicine. Its supporters may argue that it is more artful than face-to-face and hands-on medicine. Whatever we prefer as clinicians, we should strive to emphasize clinicoanatomic correlation in our teaching and convey the joy of a successful diagnosis based on traditional knowledge of anatomy. Such thought should, of course, precede the ordering of advanced imaging. In a recent survey of neurology training programs in the United States, 86% of program directors considered a rotation through neuropathology essential (Rayi, et al, 2020). Let me add my voice to this goal.

Figure 4. Kevin D. Barron and former trainees. From left to right; Suhandsu Chokroverty, MBBS; the late Kevin D. Barron, MD; the late Cesar Mayo, MD; AHK; and the late Artemio Ordinario, MD. The group photo was taken during the combined 1967 meeting of the American Association of Neuropathologists and the American Neurological Association in Atlantic City, New Jersey.
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