

When I look back on my life I often contemplate that I had the uncommon privilege to live many lives. In each phase of it I turned on the heel for a new start filled with welcome challenges. This way the two of us, starting with little more than the cloth on our bodies, could shape our very own life, with no advice or help, with an exceptional degree of self reliance, independence and freedom. I look back on all of that with an ever deepening sense of gratitude, also considering the many classmates who never had that chance. I am afraid it will be obvious from the start that I have nothing to say about the organization and practice of the profession. Also, what I can report is hardly a model for others.

I can't begin without mentioning my upbringing and the great influence of my father. Working as ophthalmologist in a small province hospital he became one of three internationally leading pioneers of cornea transplantation, winning the Theodor Axenfeldt Price for his improvement of surgical techniques; along with a reputation as the physician who makes blind patients see again; probable the most satisfying experience a physician can ever have. He was a man of great love and respect for nature and always found time to transfer it to me in many excursions, fostering the attitude to close inspection and investigation. This brought me up with a considerable background in the natural sciences and an eagerness to explore and understand things.

I studied medicine in Vienna and got hooked on pathology from the start. Doc. Köberle, of the morgue in the local hospital, was a wonderful, open man. For one semester I skipped lectures in Vienna and worked in the morgue. As a student I had done some 30 complete autopsies with presentation to the clinicians. On Sundays I had the entire building to myself; cutting serial sections of the aqueduct which I mounted on window glass and covered with washed x-ray films as nothing else was available under Russian occupation. When I listened to the lecture concerning coup contusions I doubted the story right away, borrowed instrumentation and made experiments. Dr. Köberle took me to a meeting in Vienna where, as a student, I gave 1950 my first presentation concerning the momentum of the brain, which became the generally accepted interpretation. I also published a few short papers on things like the hydrodynamic pressure in aneurysms; or on the production of melanin from epinephrine by pigmented neurons.

It became clear that I was destined for Neuroscience. As a displaced person, I was happy to be allowed in 1953, to work long hours as a guest, without formal appointment, at the Neurological Hospital. The head was a returned emigrant who translated his aggressions into a tyrannical system. Meeting him in the hallway one stood with ones back to the wall and bowed deeply. I learned absolutely nothing and was at the brink of becoming psychic unbalanced. In the Obersteiner Institute, where my father had worked, many years before, as a librarian to finance his studies I met Doc. Seitelberger who had just joined. One day he scolded me: "I have the impression you consider histology nothing but a method". He had seen right through me, recognizing what I wanted to do all my life. Not to be satisfied with shapes but to understand their relation to function. At this time the only bridge between histology and metabolism was glycogen and I began to investigate conditions which allow manipulation of glycogen.

In Vienna there was no hope for me at all. As I inherited my father's sure hands I decided to make a new start in neurosurgery. I surprised Prof Riechert of Freiburg applying for a residency with a list of publications. He was a well meaning chef and permitted me to use a laboratory and a technician to read biopsies. If I look back on these times I am shocked by the realisation that myelo- meningoceles were closed up without anyone in the department knowing what a Chiari malformation is, along with

its predictable hydrocephalus. In these years 1953-57 I worked long hours giving Evipan anesthesia and spending night watches, learning nothing of practicing neurosurgery. I was the odd man out in a team of permanently committed positions. But, at least, I had the use of a laboratory.

Nowadays it is impossible to get into research in the absence of all the necessary equipment. At that time the histochemical demonstration of an enzyme, alkaline phosphatase, was a novelty. Shortly thereafter a method for a Krebs cycle enzyme was published and the door flew open to link histology with metabolism. We still used unfixed tissue; I designed a microtome table with thermometry and collected a large crate of material. I had no idea that this crate was to become the life ring saving me from drowning. My situation, once more, was hopeless.

At that time the organization Paper Clip offered me a position in the USA. The organization is unjustly maligned by hate agitators. They showed me a picture of an American kitchen and offered a 2 year's contract to pick me up, lock, stock and barrel, with the option of returning me at the end. I was ready for anything. It took a long time to obtain visa for me, because of the fragmentation of the states of the Austro Hungarian monarchy placed me in a filled quota. The solution Paper C lip worked out for us was that Mrs. Friede was immigrating to the USA, taking me along as a dependent. This way we arrived, with a severe Asiatic influenza, a son of 3 years, and a 3 month baby, at Wright Patterson Air Force Base in Dayton, Ohio; the largest Air Force research facility in the United States. With all the delays involved, the project I had been requested for had run out and nobody knew why we were coming. I asked for a guided review of the gigantic centre and then begged to be transferred to the only place in which I found a microscope. The veterinarian John Price, a soft spoken Texan, and a mountain of a man, helped me. Nobody told me what to do.

What impressed me most was not so much the fabulous technology all around me; it was the low tone, soft spoken, relaxed expression of respect the way things were handled. Something I had never before experienced. I liked and respected these fine officers.

Baseline research was a legitimate activity of the centre. At a place in which oxygenation and high altitude are legitimate subjects of interest I had landed, incredibly, exactly right. I sat down to work, using John Prine's microscope and my crate of material. I had no intelligence clearance; when the need of photography came up I was given appointments to the inner sanctum of the sharp intelligence analysts reading the spy planes, working with them on the photography of my material.

At this time there was a turnover in neurochemistry. Holger Hyden weighted single nerve cells on quartz fibers and Alexander Pope analyzed the composition of the cortex in series of thin slices. In this atmosphere of progress it became an event when I published a series of papers in the Journal of Neurochemistry, with a complete topography of a respiratory enzyme covering the entire central nervous system of the rat. This brought me 1960 a place on the Advisory Board of the Journal.

Encouraged, I continued this line with an atlas of enzyme distribution in the brain stem of the cat. The section chiefs were impressed and they took me to the commander of the base, the legendary Colonel Stapp, a national hero who was the first man to ride a sleight driven by a rocket. The subject was outside his expertise, but the quality of illustrations impressed him enough to order the payment of the printing of my atlas at the expense of the United States Air Force. There was also a scientific gain in it: Enzyme activity was closely linked to capillary density; beyond that the activity was not confined to the pericaryon; it opened the mind to the metabolism in the so-called neuropil of

dendrite ramifications; a good thing to know that Nissl stains show only half of the picture, and, sometimes, it's the less important half.

A neurosurgeon at the center had a terrible project on cranio-cerebral trauma. At that time it was generally accepted in neurology that concussion represents a trauma of the brain stem. My examination of the tissues showed that the flexion of the cranio-cerebral junction over the dens as the critical event. In Wright Patterson this information was eagerly accepted and it led, eventually, to the neck supports of the pilot's helmets and of the helmets of the race drivers. After 2 years of work, 1957-59, the commander Lt. General USAF B.A. Schriever handed me the Outstanding Civil Service Award. I had established myself for a safe and comfortable civil service track, selecting my own line of work, in the United States Air Force. My way was free, but it was not the track I had envisioned.



Receiving the Distinguished Service Award by Commander Lt. General Schriever - 1969

At this time the concept of axonal transport, proposed by Paul Weiss, had been confirmed using radioactive markers. I used my first presentation at the meeting of neuropathologists to show how redistribution of enzymes in the axons participates in this transport. This helped me to obtain an appointment as an instructor (1959) and assistant professor of histochemistry (1961) at the University of Michigan Ann Arbor; and to my own laboratories in the Mental Health Research Institute. I had to pass the new foreign medical graduates examination at which more than 2500 failed and, after that, ten years after my promotion in Vienna, I enlisted with the students of Indiana State University to pass the examination to obtain my MD degree, followed by licenses to practice medicine in the states of Indiana, Ohio and Michigan. (Thinking back it's amusing to observe the

difference between a degree actually earned and one adopted by translation. No harm done, but it's a difference of attitude).



Above: THE UNIVERSITY OF MICHIGAN MEDICAL CENTER — 1959

The University of Michigan Medical Center - 1959

In the Mental Health Research Institute I succeeded to secure a rather large NIH grant for the investigation of the chemical topography of the human brain, giving me considerable freedom to work independent. And I learned that it did not matter what one receives; what matters is what one gives. The understanding of loyalty as a two way road which, by necessity, must start from the top. This creates happy, interdependent crews and lifetime friendships. The 1966 publication of *Topographic Brain Chemistry*, reviewing the entire literature, was the product of these years. Had I remained in Ann Arbor the next challenge on the horizon was an atlas showing the distribution of chemically different pathways and transmitters. A first step in this direction was the radiographic demonstration of catecholamine receptors on nerves cells.

To establish myself in neuropathology I was short of time in general pathology. I accepted an agreement according to which I had to work, before noon, as a first year's resident under direct supervision of a second year's resident. In the afternoon I could work across the street running my laboratories as an assistant professor. This was enforced to the letter and I found myself under all eyes observation. One of these days Dr. French, the impressive imperator and director of the largest pathology in the United States walked by my desk and said, "You know, Friede, everybody likes you." That, in turn opened the door for an associate professorship in neuropathology and passing the examinations for a diploma in Neuropathology. This time, spent out of my line, was valuable experience. I learned other ways of communication. Every biopsy was read by two pathologists; in case of doubt it was shown to the chief whose door was always open. One could also write "departmental opinion is divided". Such instances were discussed at conference with the clinicians and the thorough and considered way Gus Abel handed this was impressive. This period had a profound impact on how I see myself and the world: adopting the wisdom grounded in the Midwesterner's life on the prairie like: "You can take them to the water, but you can't make them drink" or "Give him enough rope and he will hang himself" or "I could not be fair if I talk about it know". But also: "A man can't be stopped if he knows what he wants and knows how to get it". And, finally, the most severe condemnation of a person was "I would not like to have him as a friend".

In And Arbor I presented cases to the department of neurosurgery and the regular attendance of Elisabeth Crosby made them the most remarkable case presentations I ever experienced. As everything was shown and discussed Dr. Kahn, the head of Neurosurgery said: and now Dr Crosby will inform us about the anatomy. The feeble old lady, the greatest comparative neurologist that had ever lived, gave a breathtaking discussion of the lesions. One time she broke a leg and recorded her lectures from the bed. She was a generally adored icon of excellence. (In her 1962 Correlative Anatomy there is a section in which she illustrates and describes the open ends of the myelin sheath at the nodes, defining them as equivalents of the outer mesaxons. This stunning early understanding of the of the sheath has been ignored throughout the literature of electron microscopy).

In this atmosphere of cooperation I was approached about a possible return to neurosurgery. Considering my age, my family and the heavy burden of long days and nights as a neurosurgery resident I had to decline; but to think it all through creates a weird mental experience. What would have happened? All the events described in these pages ,below this line, would have vanished, would never happened at all, as if the cassette taken out of the recorder is getting replaced with another one, completely different . Maybe the small farm I always looked for, breeding lamas? Time to think of the dealings of fate and the weight of what we hold for our free decisions.

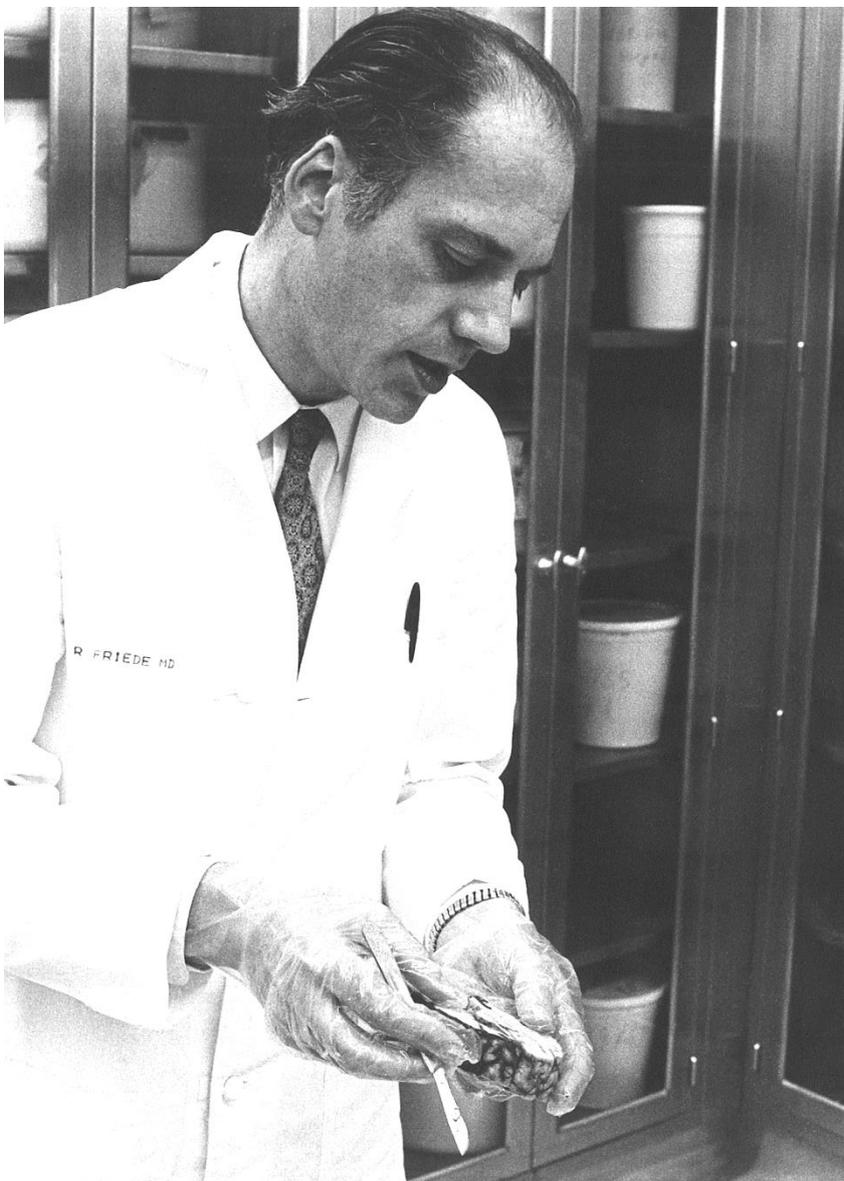


The Institute of Pathology CWRU Cleveland

In 1965 I arrived as a tenured, full professor of neuropathology at Case Western Reserve University. The first question they asked was "Do you want the babies?". There was a rich and extremely interesting supply of cases. I was familiar with all the residual lesions. Here I was offered an opportunity for a systematic exploration of the early lesions on which there was much less

information. I jumped at it. Developmental Neuropathology (first published 1975) became at this very moment my commanding activity. I never again worked with histochemistry.

At CWRU there was a strong drive for excellence. "We will be excellent or we won't be" was the attitude of the faculty with 40 applicants for every admission. The chairman was primus inter pares. Next to the service in neuropathology I started two baseline research programs. One concerned the footplates of astrocytes, which had intrigued me for a long time. It was a sophisticated program, albeit later neglected and forgotten because I was not mentally prepared to accept the data for what they showed. This is a serious problem in research. Some apparently meaningless findings can become understood only after long times of reconsideration. For instance. Did you ever ask why alkaline Phosphatase is most active at a pH which never occurs in the body? The answer is: this enzyme works as a marker of surface potentials because a surface potential is identical to a surface pH. It's as simple as this. It reminds one of the charming old German song of us making fun of the missing half of the moon because our eyes don't see to other half. Oh yes, lest I forget, myelin is the tightest package of surface charges which we can't see with the microscope.



At the brain cutting at CRWU

My second baseline project concerned myelination. In 1966, in Ann Arbor, I was impressed by the observation that the timing and the progression of myelination proceeded undisturbed in the stretched and deformed white matter; the centrum semiovale being stretched to a thin membrane. This was like a perverted experiment made by nature and only a tightly controlled function could survive undisturbed. This problem captivated my mind for the rest of my life. My first investigation in Cleveland, with my good friend Thadeus Samorajski, indispensable for his electron microscope, was a baseline investigation of myelination of peripheral nerves fibers when there was little interest in this matter. It took me 52 more years to put all of it together.

My call to the University of Zürich began with a grotesque comedy having rather unpleasant consequences. The neurosurgeon, Prof. Yasargil, was dissatisfied with the biopsy service and the department of pathology was looking for a neuropathologist to serve as an Oberarzt. As none could be found, for the conditions offered, the decision was to upgrade the position and look abroad. One of the pathology professors proposed one had to look at the candidates at their place of work. This good man travelled to Cleveland, Indianapolis and San Diego. Visiting Cleveland he looked at the building without asking me any personal questions nor a curriculum. Obviously that was all the information given to the government. It still surpasses my comprehension how a naïve man could travel visiting top universities to upgrade his department. All three of us were convinced by rumors that the affair concerned the creation of a new department. If this story sounds improbable how improbable is it that Peter, as chairman of the department never got over it that the Zürich dean's office called him welcoming him for a second place of an associated professorship. My own role is no matter of pride. When I asked what the position was I was told "Ausser planmässiger Professor" I understood that "ausser Plan" meant the creation of a new professor. Little did I know that in Zürich the designation ausserplanmässiger Professor is that of an associate professor. The disastrous procedure had not filtered down to the working level so that, upon my arrival, I was asked to register incoming biopsies. In a relatively short but for me emotionally extremely trying period of my life I could achieve that neuropathology in Zürich attained the status of a full professorship.

Arriving at empty rooms with no predecessor or preparations was just about the kind of challenge that I enjoyed. And I decided I do it all MY WAY. When asked what brains I wanted to work with I answered. "ALL OF THEM". With the cooperation of the Oberärzte ("From him one always gets an answer"), who were all on my side, I organized a new approach: Every resident had to learn how to properly dissect a brain; how to properly lay it out on a tray; to draw the lesion in our CWRW forms. He then had to present the clinical history of the case. While he was taking I inspected the material and challenged his statements whenever I noticed a discrepancy. Then I selected cases for conference, or for further workup, and dictated my exact formulation of the diagnosis. One important consequence of this method was that Wernicke, amenable to treatment, was never diagnosed; and Parkinson was diagnosed all too often. Beyond that I saw an incredible variety of lesser lesions which normally did not come to the attention of a neuropathology service. Old contusions, states after fat embolism, osteolipomas, arachnoid cysts, and so on. In the 7 years I inspected all the brains originating from the right bank of the Limmat with a generous addition of consultations from the left bank; I never counted it but it's likely in the four digits.

I introduced case presentations to the joined departments of neurology and neurosurgery, carefully balancing my rich material so that every group would occasionally see lesions out of their field

without losing interest. Prof Baumgartner and Prof Yasargil, named one of the most important neurosurgeons of the century, attended with all the staff of their departments. It was a pleasure to serve them.

I also decided to teach neuropathology in an unconventional way aiming at the needs of a practical physicians. I started out by telling them that I report common lesions which many of them would treat or even experience themselves. Then I went at length to make them understand anatomy and of disturbances of circulation, and their different manifestations; of cranial trauma; disturbances of the circulation of CSF, space occupying lesions, and so on. It was a large auditorium and it was filled to the last seat with all the stairways sitting with students. All pleasant smart young folks. When it came to examinations there were three professors to give them and the candidates would never know who was there when the door opened. I examined neuropathology and in these years only one sad fellow failed; much to the grumble of the other professors. Compared with this lecture I had only contempt for the slide sessions which give nothing they can use in life.



At a guest lecture in Hokkaido

My problem was to conduct research along with such a load of ongoing activities. Internode geometry and the design of nerve fibers requires large amounts of tedious morphometry. I realized that the school of dentistry produced many ambitious dentists who desired to better themselves with a Doctor's degree. For them it was extremely difficult to find a theme. They were conditioned to work on small objects and were good with their hands. Forming relations with dentistry I offered a program of investigation in which a degree was obtainable with a predictable effort in a predictable time. It was overrun. One candidate would work on the phrenic nerve of the rabbit, one of the

intercostals nerves of the rat and so on. It was a delight to work with them, at no cost at all; and I could reserve my means for more involved projects. In this way, carefully planning each investigation, I was able to assemble the huge amounts of data which, put together, form a compelling documentation of the role of internode geometry in nerve conduction. It was obtained by dentists. To settle my mind I read the habilitation of a Göttingen professor and found it contained less work and less substance than any one of these small dissertations.

In Göttingen I found exceptional facilities and time to work on the second edition of Developmental Neuropathology. But the academic situation in this highly politicized university was strange to me. I learned more on human nature than I ever cared to know. A DFG expert told me, at the welcome, that what I had planned to do they had solved a long time ago. An embryologist used almost verbatim the same formulation. Another professor discussed my arrival in my presence on the phone and said loud enough so that I could hear it: no, no he is not a bullshit artist; C3 and C4 professors formed opposing camps and the chancellor sympathized with political demonstrations in the Klinikum; at meetings a professor lambasted on the danger of sunlight for melanoma while all the time, and every time, puffing away his cigars. To remain in that style, at a dinner, a C3 professor reached under the table for the knee of Mrs. Friede.

I realized that even so disgusting a situation had its opportunities. With so much style, wisdom and superiority already available at this university there was really nothing I had to offer. I could ignore all of it, withdraw, being free to devote all of my attention to my work. Again I started two baseline programs. One was on macrophages and myelin using two contrary approaches. One approach was to keep the macrophages out of myelin using Millipore diffusion chambers of different pore size. The complementary approach was the development of an in vitro model to expose myelin to macrophages. It was a success. The other program was the collection of more experiments useful for understanding conduction properties of fibers. Indeed my list of 266 publications comprises mostly experiments. Residents received 2 year contracts along with the responsibility for a prepared research project. I, for myself, felt that a resident should be able to show a publication for his time in neuropathology. This approach quickly exposes incompetence, avoiding waste. The system was productive up to the last critical data using cationized ferritin, immediately before retirement, when the chancellor informed me of my own curriculum and a clerk of the administration collected my key to the laboratories. For the first time in my life I was completely free.

Upon my definitive departure from neuroscience I like to leave behind what I learned about the construction of internodes and of their role in impulse conduction. The development of peripheral nerve fibers involves interdependence between the time of Schwann cell recruitment during myelination and the elongation of the nerve. This adjusts the number and the length of internodes to the length of the fiber. Saltatory conduction in longer nerve involves longer saltations; this makes internode length a factor determining conduction velocity (The significance of internode length in saltatory conduction. Looking back at the age of 90. JNEN 76,258-259,2017)

The myelin sheath provides some insulation for the conduction of impulses by means of its major dense line. Its intermediate dense line is a conducting slit which attracts and redistributes cations along the length of the sheath, with open ends near the nodes. This combines, in a stunning design of efficiency, within one and the same structure, insulation with a coaxial conductor for the length of the internode. The proportions of sheath and axon match the proportions of coaxial cables used for

high frequency transmission. This corrects a fundamental misunderstanding of the physiology of impulse conductions (A different understanding of myelin. A legacy. (JNEN 76, 981-982, 2017).



President's Guest Speaker at the Japanese Congress of Neuropathology with Prof. Ishii President of the society – 1980

After reading the preceding pages one would not expect us to settle down in retirement tending a stamp collection. Indeed we led a very active life. Every fall we traveled the West of the United States between the Grande Sonora desert and the Canadian glaciers; however not the way tourists do it. We know and love the country where we feel at home and we enjoy the feeling of freedom and independence traveling without a fixed plan under a wide, ever receding horizon; stay at a quiet place and be gone like the wild goose in winter. At home there is much to see or visit within a day's

excursion. I also read a lot making up for the time when my reading was confined to neuroscience. Finally, close to retirement I became aware, by accident, of the Canadian Wildlife artist Robert Bateman and his incredible skill and compelling art to produce a life animal. He made me try and I was surprised that I, without any preparation, found painting just as easy as writing. But that was not enough. I decided to develop a technique which combines the advantage all three art forms. The rich color of oil; the lightness and translucency of watercolor and the accuracy of drawing. I did some 70 paintings of animals and landscapes that way, strictly for our private enjoyment.



Molas Pass – San Juan Mountains

[Reinhard L. Friede, M.D. – Curriculum Vitae](#)