Special Article

Isabelle Rapin: An Autobiography

Isabelle Rapin, MD

I was born in Lausanne, Switzerland, the eldest of three children, to a Swiss father and an American mother. My mother, who belonged to a close-knit Connecticut family, met a young professor of French when she spent a summer in Lausanne as a Vassar student. They were engaged during the winter she spent at the Sorbonne in Paris after graduation. Thus, I grew up in a bilingual home lined with books, where reading aloud in French or English, listening to music, and talking to interesting guests from many countries invited to tea or dinner were commonplace. A major focus of my teens was Girl Scout meets and camps, when I did not have my nose in a book, that is. Although Switzerland was surrounded but spared by World War II, those 6 years were marked by hateful winters in a cold house with a depressed mother cut off from her family.

My parents took it for granted that my sister, my brother, and I would attend the university. My sister became a research biologist and my brother a professor of mathematics and computer science. This bent toward science was unexpected as the background of both of my parents was literary. My mother had majored in drama, and my father's intended doctoral dissertation on Willa Cather was published by McBride & Co., NY, in 1930—"intended" thesis, because the then professor of English did not deem it acceptable on the grounds that it was devoted to a living American novelist rather than an English author. Maybe my brother's, sister's, and my doctoral degrees somehow made up a bit for this injustice. Ironically, in 1957–58, after a sabbatical in the United States, my father taught the first course on American literature at the University of Lausanne, where he eventually became titular professor of English. The Faculty of Letters in Lausanne now has a professor of American literature.

As was customary at the time, I attended all-girls' schools from ages 9 to 19 years. The last 3 years were a wonderful experience for me: I had transferred from a small school to a public academically stratified gymnase with marvelous, mind-stretching professors and many friendly and brilliant students. Among 24 women in my immediate group, 3 became physicians, 1 a chemist, 1 a chemical engineer, and 1 a professor of Greek and Latin and 1 of mathematics. As I recall, there was a future librarian, a sociologist, an administrator, and two business women.

I was interested in science from an early age and had read of the difference between active and passive immunization before age 10 years, when I decided to become a physician. I started the 6½ years of the Lausanne medical school in 1946, one of probably a dozen women students in a class of maybe 100. The class included many foreign students, in particular from the Middle East, especially from Israel, which did not yet have a medical school (I recall a

Figure 1. Dr Rapin.

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historic fist fight between an Israeli and a Syrian student at the time of the 1957 Middle East war). There were also a number of American Jewish, Black, or Hispanic students, seasoned GIs who had not found a place in an American medical school. In general, the women did well, which one of our male classmates attributed to the fact that the women had more time for study than the men did.

We were introduced to *Drosophila* giant salivary chromosomes, the cutting edge of the genetics of the time, by the exciting professor of zoology, who had historic battles over the existence of the Golgi apparatus with the professor of botany who could not find it in plants. Our professor of histology and neuroanatomy was a Lithuanian neurologist who imitated tabetic sensory ataxia and used the corner of his apron to demonstrate the folding over of the hippocampus. Attendance at classes was not compulsory, and I often found myself poring over neuroanatomy books in the library rather than in the lecture hall. The neuropathologist who asked me to translate into English a paper on the pathology of ependymomas and choroid plexus papillomas gave me as a "dictionary" the 1939 Bailey, Buchanan, and Bucy book, *Intracranial Tumors of Infancy and Childhood* (still on my shelf today), which described 100 consecutive case histories. I devoured the book as a novel. By my first rotation on the medical wards, I noted that I lavished more effort on neurologic cases than others, which confirmed my resolve to become a neurologist.

In 1951, I spent 6 weeks in neurology at la Salpêtrière and another 6 at the Hôpital des Enfants Malades in Paris where I attended the Wednesday morning public consultations of Professor Stéphane Thieffry, my first encounter with a child neurologist. I came back from Paris with my mind made up: I was to become a neurologist for children. By the way, it may be significant that another student of my vintage also opted for neurology and became the well-known professor René Tissot of Geneva, a pioneer in biological neuropsychiatry. Somehow, our education in neurology must have been right, even though there was no separate neurology service and only one full-fledged neurologist on the faculty, Dr Michel Jéquier, who, I believe, was flattered to have my thesis to direct and who lavished a great deal of attention on my fledgling effort.

The Lausanne professor who conveyed the message that medicine is a vocation was, surprisingly perhaps, the professor of surgery, Dr Pierre Decker. Not only did he discuss the current literature explicitly (we studied medicine in textbooks and lecture notes, and I was ignorant of *Index Medicus* until I started work on my thesis), but he always finished his review of the differential diagnosis and treatment options for a patient he had demonstrated to the class by asking us whether the proposed therapy was effective and, above all, appropriate to the circumstances of that particular individual, whom, he said, he was bound to meet again in our small country. His delicacy toward patients who had consented to be demonstrated to the class in the large amphitheater where he lectured left an indelible impression on me.

There was no opportunity to get a paying job as a house officer in Switzerland when I graduated in December 1952 except in psychiatric or tuberculosis hospitals, whereas house officer jobs were known to be plentiful in the United States. Aware of the names of only a few prestigious hospitals, I naively wrote to Harvard, Yale, and Johns Hopkins medical schools and to Bellevue Hospital (who knew of New York University in Europe?), saying to myself that I could always lower my sights later if need be. To no one's surprise, I never heard from Harvard, Yale, or Johns Hopkins, but I was amazed to get a telegram from the chairman of pediatrics at Bellevue Hospital, long before I had taken the last of 24 required oral final examinations, offering me a position in pediatrics for July 1, 1953.

What a break for me! Little did I know that Dr L. Emmett Holt Jr went out of his way to assemble a cosmopolitan house staff. The year I was in Bellevue Hospital, there were several Filipinos, a South African, a New Zealander who was to become the distinguished pioneer neonatologist Dr L. Stanley James, two Swiss, a Greek, an Irani future chairman, a Dutchman, and others.

I needed a doctoral degree, which is not bestowed to Swiss students at the end of medical school but requires a thesis. As I figured that an MD after my name would be required in the United States, I spent the 6 months after graduation reviewing the charts of 120 fatal epidural and subdural hematomas coming to autopsy between 1942 and 1952. With significant editorial help from my thesis director, which took some time, it was published in 1955 in the *Swiss Archives of Neurology and Psychiatry* when I received the MD from the University of Lausanne (in addition to my 1952 Swiss Federal Diploma in Medicine).

Continuing the policy of starting by aiming high, once at Bellevue Hospital I found out about the New York Neurological Institute at Columbia-Presbyterian Hospital and applied for a residency. Luck helped again: one of the attendings who interviewed me was Dr Sidney Carter, an adult neurologist whom Dr H. Houston Merritt had appointed head of child neurology when the need for that subspecialty became evident. Dr Carter's interest must have been piqued by this woman from abroad whose stated goal was child neurology. Anyway, I was offered a spot in the residency. I started on July 1, 1954, and shared my ward with Dr Robert Katzman, whose knowledge of the neurologic complications of alcoholism astounded a former pediatric intern (he had trained at the Boston City Hospital with Dr Maurice Victor and had been a student of Dr Raymond Adams at the Massachusetts General Hospital). Dr Dominick Purpura also started that July 1, but as a 6 months' rotator to neurology from neurosurgery; Dr Lawrence Poole, professor of neurosurgery, then let him take a research elective in the neurophysiology laboratories with Drs Eli Goldensohn and Harry Grundfest, and that was the end of his clinical career. Dr Charles Poser, to become well known for establishing criteria for a diagnosis of multiple sclerosis, was one of the chief residents, and Dr Joseph Marotta from Toronto was the other. Dr Robert Fishman "carried Dr Merritt's bag" (ie, he

took care of all of Dr Merritt's patients as Dr Merritt, with his computer-like mind, diagnosed them on the basis of one look and the chief complaint). Drs Labe Scheinberg, James Austin, T.R. Johns, and William Sibley, all future academicians, were senior residents. Among eight first-year residents, we were three women; there were none in the years above us. Drs Niels Low, Elliott Mancall, Elliott Weitzman, Rosalie Burns, John Menkes, John Freeman, Richard Allen, and Peggy Ferry were some of the other future academicians who overlapped my years at the Neurological Institute. I also met Dr Alan Aron, then a medical student who rotated on our service, who started child neurology at Mt Sinai Hospital in New York.

Knowing I was going to be a child neurologist, I took two 3-month rotations on Dr Carter's service, located in a small ward in the Neurological Institute at the time, and attended the child neurology clinic on Wednesday afternoons. The National Institutes of Health established training programs and requirements for child neurology in 1956. I was supported by this National Institutes of Health training program for a fourth year during which I attended pediatric neurology ward rounds with Dr Jim Hamill or Dr Carter and Dr Carter's Wednesday morning outpatient rounds for children with cerebral palsy and those with speech and hearing disorders. The latter intrigued me, as what ailed these nonverbal children was not obvious. (I found out later that behavioral audiology was unreliable at diagnosing the severity of hearing losses in very young children, and, in retrospect, that autism would no doubt have been the correct diagnosis in some puzzling "emotionally disturbed" mute children.) I had already become interested in aphasia (I had actually diagnosed a classic case of alexia without agraphia in my first year, not realizing how rare it is), but these children were more challenging. During this fourth year, I also read the electroencephalograms (EEGs) for Dr Goldensohn's epilepsy clinic, which I attended, and remember vividly teaching EEG interpretation to Dr Burns and others.

That year, I got my feet wet in clinical research under the mentorship of Richard Allen Chase, at the time still a medical student who had his own National Institutes of Health-supported laboratory (*sic*) in the Ear, Nose, and Throat department. He was investigating the effects on motor control of finger anesthesia and of delayed auditory feedback of clicks produced by key tapping. He introduced me to St Joseph's School for the Deaf in the Bronx where we went to determine whether we could use the delayed auditory feedback of clicks as a more objective test of hearing than behavioral audiometry.

The Albert Einstein College of Medicine of Yeshiva University enrolled its first class in 1955. Dr Saul R. Korey recruited Labe Scheinberg in 1956 (after he too "carried the bag" for Dr Merritt), Bob Katzman in 1957, and Elliott Weitzman 2 years later. Labe invited me to visit him in February 1958. Dr Goldensohn lent me his car (a rather dilapidated Studebaker), which stalled in the rain on Tremont Avenue in the Bronx and required a quick battery recharge before I could get back on my way. Naive once again, I was almost tongue-tied when I found myself being interviewed by Dr Korey for a faculty position in child neurology. Anyway, I came back for a second visit and started at Jacobi Hospital in September 1958 (September, not July, because I had gone to Europe for 3 months in the summer of 1957 to celebrate the end of my residency, as I had been away from home for 4 years).

Dr Korey took it for granted that all of us would combine research with clinical work. The question was not whether we would do research, but what kind of research we would do. He had already recruited a strong neuropsychologist, Dr Louis Costa, from whom I learned a great deal and with whom I collaborated to study the developmental disorders that were to become the focus of my work. Dr Korey was such a charismatic chairman of neurology (tough but supportive of his faculty, utterly honest, and an excellent clinician as well as an inspired investigator of basic disease mechanisms in the nervous system) that the strong group of clinicians and investigators he assembled for his department remained for more than a decade after his untimely death from cancer at age 45 years in September 1963, an irremediable loss to neurology and to me personally.

I met my husband, Harold Oaklander, at the time a graduate student in industrial relations at Yale University, in August 1958 at a general semantics seminar at Bard College, not far from the Dutch stone house in Coxsackie, NY, built in stages between the 17th and 19th centuries, which we were to buy in 1962 and have been restoring ever since. We were married the following spring. Harold stated that he had always hoped to marry a professional woman and invented "women's lib" before the term was coined. Without his unselfish and sustained encouragement and help, his willingness to share in all household and child-rearing jobs (except for car maintenance, his, and sewing, mine), I could never have flourished in child neurology as I did. Also critical was the remarkable baby sitter, Ms Evelyn Barnes, whom I inherited from Dr John Menkes when he left New York to take a job at Johns Hopkins Hospital in Baltimore, for which I thanked him daily for the 6 years we enjoyed her help. Rather than taking an industrial or teaching job outside of New York after he got his PhD from Columbia University in 1970, my husband accepted a faculty position in the graduate school of business of a less prestigious institution than mine because he knew I could not bear the thought of leaving Albert Einstein College of Medicine. There were some compensations to his marrying an academic: conferences abroad have enabled us to visit many interesting countries together. One of the trips introduced him to Japan; the lifetime employment and avoidance of layoff in this country have become his specialty and consuming interest.

We were fortunate to have four fine children: our older daughter, Anne Louise, an MD-PhD Einstein graduate and card-carrying neurologist, currently a faculty member of the pain service at the Massachusetts General Hospital and the mother of our two grandchildren; our second daughter, Christine, a PhD in art history in Delaware who is finishing a book on the art scene in New York at the turn of the

century; our older son, Stephen, an executive in a record-producing company in New York; and our younger son Peter (middle name Roy, for Dr Saul Roy Korey), an electronic engineer living in the Orient for several years, who is his company's sales representative for Southeast Asia.

After I came to Albert Einstein, I started out by taking service on both adult and child neurology, splitting the latter with Dr Lawrence Taft, who ran the Children's Evaluation and Rehabilitation Clinic in the Department of Pediatrics. Our Child Neurology Service, which now counts 8 faculty members, has trained over 70 child neurologists. Several are academicians, including at Harvard, Yale, Robert Wood Johnson, and Thomas Jefferson Medical Schools, Miami Children's Hospital, and the Ramathibodi School of Medicine in Bangkok, Thailand.

In 1959, I obtained my first National Institutes of Health grant to continue research at St Joseph's School for the Deaf. The first computers to record event-related potentials became available in the early 1960s, just in time for me to apply this technique to the diagnosis of deafness in the children born of the major rubella epidemic of 1964–65. As a by-product of my interest in deafness, I met and was instrumental in attracting to Einstein in 1958 Dr Robert J. Ruben, its first and most distinguished chairman of otolaryngology (he and his colleague, Dr Thomas Van Der Water, developed techniques for growing embryonic cochleas in vitro, which has enabled a series of studies on the biologic basis of hearing loss and, potentially, its mitigation by regrowing hair cells). Dr Ruben and I have shared in the care of many deaf children. Most were referred to him; some I saw at St Joseph's School, where I remain a consultant to this day; and many were sent to Einstein because my laboratory was the first in the New York area to offer an electrophysiologic test of hearing. After brainstem evoked responses came onto the scene in the early 1970s, electrophysiologic audiometry became audiology's turf. By then, I had become fascinated with developmental language disorders and autism and did not have the imagination to see how I could apply event-related potentials to the study of language, so I left the field of electrophysiology in 1974.

My interest in language disorders and autism was enhanced by the arrival at Einstein of Dr Doris A. Allen, whose background was developmental psycholinguistics, psychology, and speech pathology. She had taken over the directorship of the Albert Einstein Therapeutic Nursery in the Division of Child Psychiatry, where she educated preschoolers with language disorders and behavioral or autistic behaviors, together with their parents. Dr Allen learned about the neurologic basis of language from me and I learned about linguistics from her. Together, we proposed a classification of developmental language disorders and determined that autistic children were truly dysphasic as well as autistic.

In the late 1970s, the Child Neurology Society charged a group of us with developing a neuropsychologically based classification of the developmental disorders of higher cerebral function. We presented a "seat of the pants" proposal to the annual meeting of the Child Neurology Society in Minneapolis in 1981. In 1985, our group obtained a multi-institutional, multidisciplinary grant to develop an empirical nosology of autism and developmental language disorders, of which Dr Ronald David of Richmond, Virginia, was the first principal investigator. I succeeded him in 1988 for the school-aged follow-up of the cohort of close to 500 children we had studied at preschool ages. In 1996, our group published a monograph, *Clinics in Developmental Medicine #139, Children With Inadequate Communication: Developmental Language Disorder, Autism, Low IQ*, which describes the preschool phase of the study. We are still working on publishing the data from the school-aged phase of the study. A spinoff of the Child Neurology Society's charge was to be selected, together with the neuropsychologist Dr Sidney Segalowitz, as editor of the child section of the *Handbook of Neuropsychology*, an interesting and challenging experience.

After evaluating hundreds of autistic children, I became convinced that the report by one third of parents of autistic preschoolers of a very early language and behavioral regression is real and deserving of biologic investigation. Autistic regression overlaps with the much rarer acquired epileptic aphasia (Landau-Kleffner syndrome) and with the disintegrative disorder of the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (*DSM IV*), both of which I had studied earlier. It has taken many years and several descriptive studies to enable us to devise a fundable study of language/autistic regression. Encouraged by the National Institutes of Health, Dr Shlomo Shinnar and I are currently preparing an application for a multi-institutional treatment trial of children with language loss, the great majority of whom were or became autistic following the regression, the cause of which is just as baffling now as it was 10 years ago.

The accepted lore is that, in order to be productive in research, one should have a narrow focus. I must confess that, inspired by my first chairman, Dr Korey, and by the children who have walked into my office or clinic over the years, I have not been able to give up my interest (hobby?) in the investigation of the neurologic genetic/metabolic diseases of childhood. In the late 1950s, Dr Korey had envisioned the power of a joint neurochemical and electron-microscopical study of human disease, which has borne rich fruit in the dementias and in the lysosomal storage diseases. I vividly remember the day when Dr Robert Terry showed us the first electronmicroscopic pictures of the membranocytoplasmic bodies in Tay-Sachs disease (up to then, storage was thought to be pure ganglioside and amorphous), pictures so beautiful that they were hung in the Museum of Modern Art in New York City. Because I stayed in one institution, I was able to follow a number of undiagnosed patients to their demise and pathologic diagnosis, with resultant accrual of novel information. The course of meganeurite development in a variant of Tay-Sachs disease came to light in one of my patients, first biopsied and then autop-

sied 2 years later. Findings contributed by this one 3-year-old little girl have spawned an entirely new field of research that continues to this day. Another peak experience was the afternoon when Drs Sidney Goldfisher, Cyril Moore, Anne Johnson, Lawrence Gartner, and others met in a seminar I organized to discuss one of my patients, who had died of Zellweger disease. It was on that day that the lack of visible peroxisomes in the liver and the respiratory chain abnormalities in mitochondria came to light, a finding that marks the inception of unraveling the neurologic peroxisomal diseases. Selective destruction of the dentate nucleus without pathology anywhere else in the brain resulted in the most severe myoclonus I have ever seen, which rendered an intelligent little girl with Gaucher's disease completely helpless and mute. Just in the past weeks, it was reported that Alexander's disease results from de novo dominant mutations in the gene for glial fibrillary acidic protein and not from an enzyme deficiency. The first step toward this discovery was taken 15 years ago, when the parents of one of my patients insisted that this clinical diagnosis be validated with a brain biopsy, in which the neuropathologist Dr Anne Johnson discovered an accumulation of filaments in astrocytes. It is impossible for me not to view such extraordinary cases, which come unsolicited to my office with symptoms I could not imagine existed, as mandates for investigation. And they surely add spice to life!

Because I entered a nascent field, I have been privileged to be a founding member and serve the Child Neurology Society and the International Child Neurology Association, through which I have made many friends in many countries. I was also fortunate to be invited to serve the American Academy of Neurology and American Neurological Association. I was honored to sit on grant review committees for the National Institutes of Health and the March of Dimes and, most enjoyably, to serve as a member of the Council of the National Institute of Neurological Diseases and Stroke. Teaching generations of students and residents is a joy and has forced me to stay somewhat current in broad aspects of clinical neurology and at least conversant with neuroscience research.

The message I would give a young colleague is that child neurology is a wonderfully rewarding field, intellectually and personally, because of the families you will meet. In order to have it all, that is, be married, have children, restore and furnish an antique house, work in the garden, enjoy a lot of what life offers, and have a great job, you need a supportive and generous mate, adequate baby sitting and house help, flexibility, good humor, and a nose for the unusual. Consider every patient a potential source of new knowledge, describe what you see, pursue your interests vigorously, and learn to cut corners and prioritize. Find a good mentor, enjoy what you do, and be lucky.