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## Anne Buckingham Young

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# Anne Buckingham Young

**Born:**

Evanston, Illinois
December 30, 1947

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Vassar College, Summa Cum Laude, AB (1969)
Johns Hopkins University Medical School, MD (1973)
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**Appointments:**

Assistant, Full Professor of Neurology, University of Michigan (1978–1991)
Julieanne Dorn Professor of Neurology, Harvard Medical School (1991–2012)
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**Honors And Awards (Selected):**

Member, Institute of Medicine (1994)
Fellow, American Academy of Arts and Sciences (1995)
Dean's Award for Support and Advancement of Women Faculty, Harvard Medical School (1999)
Marion Spence Faye Award for Women in Medicine (2001)
President, American Neurological Association (2001–2003)
President, Society for Neuroscience (2003–2004)
Fellow, Royal College of Physicians, England (2005)
Milton Wexler Award, Hereditary Disease Foundation (2006)
Johns Hopkins Medical School Distinguished Alumni Award (2007)
Vassar College Distinguished Alumni Award (2010)

*As a graduate student, Young provided the first biochemical evidence of glutamate as a neurotransmitter of the cerebellar granule cells. She developed biochemical techniques to measure inhibitory amino acid neurotransmitter receptors in the mammalian brain and spinal cord. As a faculty member at the University of Michigan, Young and her late husband (John B. Penney, Jr.) established the first biochemical data that glutamate was the neurotransmitter of the corticostriatal, corticobulbar, and corticospinal pathways. They developed film-based techniques for quantitative receptor autoradiography. They also provided evidence for their most widely cited model of basal ganglia function. Their model has suggested novel interventions in Huntington's and Parkinson's diseases such as deep brain stimulation. Dr. Young has worked more recently on gene expression changes in Huntington's and Parkinson's diseases and on therapeutic approaches to neurodegenerative diseases.*

# Anne Buckingham Young

## Early Life

I was born in Evanston Hospital, Evanston, Illinois, on December 30, 1947. I grew up in a privileged environment in Winnetka, Illinois. My ancestors were pioneers who eventually made and lost fortunes during the settling of Chicago. My father was a businessman, and my mother a housewife. Both parents were interested in science, however. My father had majored in chemistry at Harvard, and my mother in physics at Vassar. In her later years, my mother edited and wrote books on science for nonscientists. *Science* and *Scientific American* were on our coffee table. Even as a young child, we were always talking about scientific issues at the dinner table. Gravity was discussed at breakfast. I have an older brother who liked math and physics. He eventually became a professor of economics and business at Johns Hopkins and at the University of Oxford. I was more interested in biology. I have a younger sister who loved animals and who eventually became a physical therapist.

In school, I was a very poor reader, never coming close to finishing the story on the standardized reading tests. Every year I was one to two grades behind in reading, but because I did well on everything else, I was passed each year. I was never given any special instruction but my slow reading has influenced the rest of my life. It was not so much reversing letters and so on but rather the words would mean nothing to me unless I said them in my head first. I had to read aloud to myself at a slow pace. I was incapable of skimming. Therefore, the fastest I can go in a fiction book is about 30 pages an hour. It has always been awkward when somebody hands me something and says, "Read this." I have to ask them to tell me what it says or be prepared to wait a while. My writing is not affected, and in fact, I am a good proofreader because I have to look at every word. I am a poor proofreader when I have to identify missing parts of sentences.

My family would spend the summers on my mother's family farm in southern Ohio. I was a tomboy and hung out doing projects with my father. He called me "Tiger Annie." My father taught me how to fight with my fists and later in life how to fight with a knife or a broken bottle. Most of the time when we were there on the farm, however, we had to entertain ourselves. We trapped snapping turtles, hunted arrowheads, built huge kites, and helped with haying and milking the cows and with feeding the pigs. Experiences on the farm gave me a fascination with biology.

I went to a small private day school in Winnetka for middle and high school. There I enjoyed science and math and avoided history courses where reading was too demanding. I also participated in all sports and was on the varsity field hockey, basketball, and softball teams. In high school, I became fascinated with DNA and memory and learning. I began to read *Scientific American* and *Science*.

When I applied to colleges, I was turned down at my first choice, Radcliffe, and instead I got into Vassar and Mount Holyoke. I decided to go to Vassar. At Vassar, I decided to major in chemistry and minor in art history and philosophy: chemistry because I wanted to be a biochemist with a solid fundamental understanding of chemistry; art history and philosophy because neither required much reading (everyone reads philosophy slowly). I did not take the freshman English course that required reading a book a week.

I went to all my classes and studied intently. I never went on any of the social "weekend" trips to male colleges—not because of studying, though. Instead, I went out with locals and played on the local sporting goods store basketball team. There were only nine chemistry majors in my class, and I was the only student interested in biochemistry. We all had keys to the chemistry building, which had a nice cozy library. I spent free time in the chemistry library reading things such as Faraday's diary. Even though I was a slow reader, I was fascinated by how he thought and planned experiments. In my junior and senior year, I had use of the entire biochemistry lab except for the one afternoon a week when it was occupied by the students taking biochemistry. For the first time, I was able to conceive of, execute, and interpret my own experiments. It was exhilarating.

I loved framing a hypothesis and seeing if I could prove or disprove it. My biochemistry professor, Anne Gounaris, was incredibly supportive and encouraging. She helped with teaching me techniques, but she also gave me a lot of freedom in the lab. We worked on pyruvate decarboxylase biochemistry. I wanted to purify and characterize the enzyme. I worked out my own colorimetric assay so I could do many samples much more quickly than the previous Warburg assay. Some of the work was published in the *Journal of Biological Chemistry*.

I decided I wanted to be a scientist—studying human disease and, hopefully, ultimately making a difference for people. I wanted to get a PhD in biochemistry from Rockefeller University. My hometown pediatrician suggested I pursue a combined MD/PhD, however. In a way it made sense because then I would be able to do research on human disease more easily. So, I also applied to Rockefeller, Johns Hopkins, and the University of Wisconsin (the latter two had good MD/PhD programs by reputation). I did not get into Rockefeller but I got into the other two programs and decided to go to Johns Hopkins University.

## Medical School

Medical school in Baltimore was very different from Vassar. The school was in one of the most impoverished areas of the city, and our dorms were in a partially protected compound. There were nine women in a class of 110. The men could belong to the all-male eating club. The first night I was at Hopkins, I was at a party at the eating club, and during the party, there were shots outside—a man had been shot. All the eager med students rushed outside to help. The man was carried to the emergency room around the corner. Later, I would find that you could tell how active the emergency room was by looking at the dripping blood leading up to the emergency entrance. Then the rain would wash it away, and the process would start over again. There were bullet holes in the windows of the laboratory where I worked.

In my first year, I went to a party at a biochemistry professor's house and he told me that he was on the admissions committee when I applied, and that they found two Anne Youngs had applied. At a special meeting of the admissions committee, they divided the Anne Young documents into two piles—one the Anne Young they liked (which was me) and the other the Anne Young they did not. However, in the middle of the table was a letter saying that Anne Young was crazy and should never be a doctor. A Vassar alum who was a doctor at Hopkins came up in the fall (before the final admissions decision) to see if it was true and decided I was okay after a brief interview. In fact, I knew this letter was about me because not only had I gotten very depressed at Vassar, but I became hypomanic and was locked up for five days in the hospital. This letter was from the psychiatrist, and it was sent in because I had naively released all my medical records for the admissions process.

Hopkins had a southern flavor and its politics were conservative. What a change from college! I gravitated to a small group of anti-war, pro–civil rights students who sat in the back of the classroom. Classes were all large lecture courses taught by men with famous names. We had our own names for all of them—such as the pulmonary professor, deadspace Sheppard. We also had some incredible lectures such as those from Richard Johnson about efforts to discover the cause of transmissible spongioform encephalopathies such as kuru, scrapie, and Creutzfeld Jakob disease. He showed us all the exotic places such as Papua New Guinea, where he had gone to study the illnesses.

With only nine women in the class, the lecturers definitely catered toward the men. In almost every lecture, nude pinups or cartoons of nude women would be shown just for entertainment. This was somewhat irritating. In my second-year radiology class, I noticed that the lecturer always put his slides into the projector before lunch for our afternoon lecture. I got hold of a full-frontal picture of a nude man, all buffed and greased on a cliff, and one day during lunch, I slipped it into the lecturer's carousel. As he lectured,

first came up the usual pictures of nude women, and then suddenly there was this nude man. The lecturer turned pale and flipped it to the next slide. All the men in the class started laughing and made him back up and show the slide for the women. It was very funny, and the lecturer never showed another nude during the course.

One of the members of the little group of liberals in the back of the lecture room was Jack Penney (John B. Penney, Jr.). He had been to college at Dartmouth and was a member of Students for a Democratic Society (SDS). We liked each other and started going out. He was from New England and most recently had lived in Newton, Mass. His father managed the parks for the town of Newton, and his mother was a dental hygienist. Jack was very vocal about civil rights but, in general, he was a quiet New Englander with a dry sense of humor. He was encyclopedic in his knowledge, had a photographic memory, and was a very fast reader. We liked the same things such as hiking, skiing, and swimming and our relationship grew. We moved in together in the second year of medical school.

To pursue a combined MD/PhD degree, I arranged to meet with the dean of students to discuss my options. Much to my surprise, he said there really was no formal MD/PhD program; rather, each individual was encouraged to construct his/her own curriculum. I asked if I could use the year and a half of elective clinical time pursuing my PhD work and still have it count toward medical school. He said yes. I asked if I could get it in writing, and he agreed.

During the first year of medical school, I looked into laboratory opportunities. I was thinking about biochemistry when a biochemistry graduate student suggested I talk to a young assistant professor of pharmacology, Solomon H. Snyder, MD, who was working on the biochemistry of the brain and the role of drugs in brain function.

I made an appointment to see him and brought with me (at the suggestion of the graduate student) a written proposal for a summer project. We talked, and he said he would be pleased to have me join the lab in the summer. A couple of weeks later, we met again and discussed my project and somehow, without even a bump in the conversation, I left the office thinking I had written a great project but that I would actually pursue an even better project instead. Talking to him was really energizing. He thinks very broadly and outside the box. That summer, in Sol's lab, I learned a whole slew of new techniques including dealing with gradients, radioactivity, and with subcellular fractionation. The people in the lab were diverse and interesting, and the problems of neurotransmitter function in the brain fascinated me. After that summer, I wanted to do my PhD in Sol's laboratory. He agreed to have me join the laboratory when I was done with my medical school requirements.

I met with the head of the department of pharmacology and asked if I could be a graduate student with Dr. Snyder and if I could count my med

school physiology, pharmacology, and biochemistry courses toward my PhD in pharmacology. He said yes. I asked to get it in writing. He said fine.

Over the next year and a half I finished up my medical school courses—nine months of basic science and nine months of required clerkships. The clerkships were medicine, surgery, pediatrics, ob-gyn, and psychiatry. I did not intend to take any elective rotations. During my medicine clerkship in the summer of 1971, Jack and I got married. We were both fascinated by the nervous system and wanted to be neurologists. Neither of us had neurologic disease in our families. We found the diseases of the brain particularly interesting and challenging. We also thought it provided a large understudied universe to explore.

## PhD Program

I started full time in the lab in January 1972. I studied homocarnosine and homoanserine in the rat brain, to determine whether they could be functioning as neurotransmitters. First, I had to devise a quick and accurate assay to measure the dipeptides. Sol was a wonderful mentor. He figured out what made each person in the lab tick. Some he punished to work harder and others he would pat on the back. He loved to look at the primary data coming out of the scintillation counter. He would ask probing questions and come up with intriguing ideas based on reading a very diverse set of topics and literature within and beyond neuroscience. He would listen carefully to my ideas as well, and conversations were always lively.

All was going well until Saturday, February 19, 1972. That day Jack and I and four friends went winter camping in western Maryland on the Appalachian Trail. The snow was up to mid-thigh and we trudged three miles only to find that the lean-to we wanted to stay in had collapsed under the snow. Back in Baltimore after a long and exhausting hike, I went out to pick up a pizza and was hit by a car as I crossed the street. I fractured my femur and cut my head. One day later, I mentioned to Jack that I was seeing things fly by my vision. I was not too concerned because I was on painkillers and I thought it was just a side effect. The second night, my roommate called the nurses twice to tell them I was having trouble breathing—nothing was done. I was supposed to go to surgery in the morning and Jack came in to see me. He found that the nurses had me in four-point restraints because I bit a nurse and pulled out all my tubes and catheters. I was gasping for air. They got a blood gas and my p02 was 40; a chest X-ray showed a whiteout and I had petechiae in my nail beds and sclerae. I went straight to the intensive care unit (ICU). It eventually became clear that I had fat emboli to the brain and lungs. (Emboli composed of blood fat occur very rarely after the fracture of a long bone.) I almost died. Jack was told I had a 50-50 chance of survival. Fortunately I lived, and after three months on crutches and a cane I could walk independently. I got back to the lab within three weeks of being home

from the hospital. I was never quite the same afterward and developed a streak of paranoia that never went away.

While I worked on homocarnosine and homoanserine, I became intrigued by the idea of using neurotoxins (the way alpha-bungarotoxin was being used to study nicotinic acetylcholine receptors at the neuromuscular junction) to measure the receptors for putative inhibitory neurotransmitters, such as the amino acids glycine and gamma-aminobutyric acid (GABA). Sol was completely supportive of my interest and encouraged me to pursue the project.

I worked across the bench from Candace Pert who was trying to measure opiate receptors using high specific activity opiate agonists and antagonists. Actually, Candace began looking at receptors because Pedro Cuatrecacas was on the same floor and he was doing work on the insulin receptor using iodinated insulin. That gave Candace the idea that she could measure the opiate receptor using a similar approach. She had done a rotation in Pedro's lab and was convinced this could be used more broadly. In Sol's lab, Shalesh Banerjee iodinated nerve growth factor to look for that receptor.

I figured that certain centrally active neurotoxins would be very potent and bind tightly to neurotransmitter receptors. At the time, researchers were just starting to accept GABA as a neurotransmitter, and glycine's role was still hypothetical. I thought that if glycine were the neurotransmitter of the Renshaw interneurons and the 1a afferent–linked interneurons in the spinal cord, then strychnine, which seemed to block these responses, might bind tightly to the glycine receptor and allow its characterization. Similarly, bicuculline appeared to block GABA receptors.

I had strychnine and bicuculline labeled with tritium by New England Nuclear. They returned a vial of 5 millicuries of brown and green material for each. After I purified the strychnine sample by thin layer chromatography, I obtained tritiated strychnine with very high specific activity. With that, I was able to show that strychnine binding was distributed in the rodent brain and spinal cord exactly as would be expected for an agent binding at glycine receptors for inhibitory interneurons in the spinal cord, brainstem, and thalamus. The purification of the bicuculline was more difficult, and the specific activity was poor. I sent off for a new batch. In the meantime, I was able to characterize strychnine binding in detail. I showed that it bound to a site on the receptor that was distinct from the glycine binding site and that it affected glycine binding allosterically. This was the second neurotransmitter receptor characterized using tritiated antagonists as labels for the receptor.

The tritiated bicuculline turned out to be unstable. Instead, we found that measuring the GABA receptor with [3H]GABA turned out not to be difficult once we had a good batch of tritiated material with high specific activity. In the last few months in the lab, I studied [3H]GABA binding the same way that I had the strychnine binding site. A medical student, Steve

Zukin, worked with me on the project. Later, as I was leaving the lab, Sam Enna came to the lab as a postdoc, and he continued the GABA project.

Jack was working in his elective time in the laboratory of Robert Herndon, Leslie Weiner, and Dick Johnson studying the virus responsible for progressive multifocal leukoencephalopathy (PML). He was able to show the virus in the spinal fluid of PML patients and identify it as a polyomavirus (the JC virus).

While he was in the lab, he told me of a graduate student, Mary-Lou Oster-Granite, who was working on a virus that killed all the granule cells of the cerebellum without damaging other cerebellar neurons. I knew Mary-Lou from anatomy because she was one of my anatomy partners when we dissected our cadavers. I thought perfect! I could collaborate with her, and we could find the neurotransmitter of the granule cells of the cerebellum. It was a project that took three weekends.

The first weekend, I did high affinity uptake of all the neurotransmitter candidates on a litter of animals without granule cells. Aspartate and glutamate uptake were the only things affected. The next weekend, I studied the kinetics of glutamate and aspartate uptake, and only the number (not the affinity) of uptake sites was affected. The third weekend, I put samples over the amino acid analyzer and found that only glutamate levels were decreased. This study was the first to associate glutamate with a particular neuron type and solidified its putative role as a neurotransmitter.

Collaborating with the neurovirologists introduced me to many of the neurologists. I also developed several other projects with others in the neurology department including with Don Price and Jack Griffin. Reading for my thesis defense also led me into many neurology journals, and I began attending neurology grand rounds and brain cutting.

Jack applied for residency in neurology and got into his first choice, the University of California, San Francisco (UCSF). He stayed with me in Baltimore for his internship. I applied for internship and residency a year later. When I came to defend my thesis, 30 months after I started in the lab, I had ten publications and I passed my oral defense without problem. Nevertheless, the pharmacology department told me that I had to stay another year in the program. I asked why, and they said otherwise it would look as if Hopkins gave out cheap quickie PhDs (I was going to get my MD in 1973 and PhD in 1974). I told them I had the letter that the department chief had signed two and a half years ago, agreeing to my proposed program. They changed their minds and gave me the degree.

## Internship and Residency

I matched to internship at Mt. Zion Hospital in San Francisco—a community hospital with a fairly good resident-run teaching service. I applied to UCSF for residency. They were dubious because I had never even taken a

clerkship in neurology. I urged the faculty I knew at Hopkins to lobby for me, and I got in.

San Francisco was a great place to do an internship and residency. The institution had outstanding neurology faculty and residents, the weather was nice, and California seemed cool—relaxed, casual, and liberal. Jack and I loved it. We bought a house up high on the hill south of the Sunset district. We rented a 20-foot sailboat with some fellow residents. We worked very hard as house staff, but we knew that our days off could be spent in some beautiful outdoor setting such as Mount Tamalpais and Stinson Beach or Point Reyes.

I started out with six residents in my class. Ed Chaplin was a pediatric neurology resident—so, in the second year, he focused on peds. One of our residents dropped out. Then Rick Rosenbaum finished early after the second year because he had had a year of time in neuromuscular already when he started. Then Seth Finkelstein left early to go to Mass General to do stroke with C. Miller Fisher. So that left two of us, Justin Zivin and me, to be the only third-year residents. I was chosen chief resident and had to organize schedules to cover all the services. It was a challenging third year made more complicated by outside events.

During my second year of residency, I became pregnant and I had a daughter, Jessica, that February. My chairman, Dr. Robert Fishman, was not thrilled. Jack and I persuaded him that we would be able to cover our duties. Jack was a year ahead of me so he was finishing his residency a few months after the baby was due. We hired a young 19-year-old high school dropout, Joan, to live with us and take care of the baby while we worked our long work weeks.

It was clear at the end of residency that the only jobs available at UCSF were low-level ones without much of a start-up package. We started looking at places with new chairs who would have good recruitment packages for two people. The University of Michigan offered us very good packages with big labs, excellent equipment, and funds for start-up and technicians. Jack was going to do one more year of fellowship with Sarah Winans Newman in the anatomy department working on immunocytochemistry before starting his lab. I was going to go as an assistant professor. We decided to take the jobs. We asked Joan, the babysitter, to help us during the move. She came, and stayed, and ended up living with us all through our 13 years in Michigan. Her presence made a huge difference to us. She became part of the family. We felt comfortable leaving the girls (we later had another daughter, Ellen, in Michigan) alone with her if we had to go to meetings together.

## University of Michigan

Sid Gilman was the chair of neurology at the University of Michigan (U of M). He was a fantastic mentor. He taught us how to write a grant, how to talk

to program people, and how to arrange a site visit. He critiqued our grants and papers. He introduced us to people in neurology and at the National Institute of Neurological Disease and Stroke (NINDS) and suggested us for talks at major meetings. He involved us in program project grants, and we not only did basic science work but we started working on positron emission tomography studies of Huntington's disease (HD).

I wrote my first grant when I was still a resident. I had been struck during my residency by the fact that neurologists and neuroscientists had not even identified the neurotransmitter of the corticospinal tract and knew little about the neurotransmitters of the local circuits in the spinal cord in conditions such as spasticity. Having worked on the glycine and GABA receptors as a graduate student, I decided to examine what happened in the spinal cord in spasticity. In those days, one could submit both a K award and an R01 at the same time. I got the K award but my score on the R01 was miserable and, I thought, not fundable. Sid told me to call up my program person who looked after the grant administratively at NINDS. Nancy Wexler was the program person! I had heard of her and her work with Huntington's disease. I was afraid to call but I mustered up the courage to do so. She was very nice. She told me that, even though the priority score was poor, my grant *would* be funded because spasticity was of interest to injured veterans. I was elated. Nancy was later to play a very important role in my life. Having gotten a grant, Jack and I decided to have another child. We had another daughter, Ellen.

Then came the experiments. They turned out to be hell for the rats and pretty close to hell for us. Rats with severed spinal cords are paralyzed, try to eat their lower limbs, and are in spinal shock for some time. We had to crede their bladders every eight hours and paint their legs to keep them from gnawing on them. On top of that, it was not easy to show any changes in glycine or GABA levels, receptors, or in turnover. I began looking for side projects.

Jack and I started working together with one of Sid Gilman's colleagues, Mark Bromberg, who was studying cats with primary motor cortex lesions. We wanted to examine his cats biochemically to identify the neurotransmitter of the corticospinal tract. Jack did the anatomy, the Fink-Heimer stains, and the punch biopsies of postmortem tissue. I did the high affinity uptake and levels of putative neurotransmitters by high performance liquid chromatography (HPLC). Glutamate was the only transmitter that fit the bill. We did the experiments in primates with Sid and glutamate again turned up as the associated putative neurotransmitter.

Sid Gilman and George Dauth were using [14C]-2-deoxy-D-glucose to measure tissue metabolism in spastic monkeys with quantitative autoradiography. We wondered if we could measure neurotransmitter receptors with film autoradiography. We needed film that could measure tritium decay, and Amersham had just come out with such. We made standards of tritium in brain paste and then plastic and worked out the methodology. We found we

could easily measure receptors in 20 micron brain sections with excellent signal to noise, excellent kinetics, and pharmacology, and with outstanding anatomical delineation. We published the methodology in 1981. The technique was the first to make it possible to measure receptor levels, affinity, and pharmacology in tiny areas in individual animal brains. It was a true advance over the prior bind-and-grind techniques.

At this time, I was hiring for a laboratory manager and lab technician and I interviewed a man named Zane Hollingsworth for the job. His ambition was to be an outstanding laboratory manager. He seemed excellent, and I hired him on the spot. Zane lived up to every expectation. He soon learned everything about the equipment in the lab but also about all the experiments as well. He made sure everything was written down in notebooks and that all the protocols were clear. He managed the students coming through the lab in terms of their use of equipment and documentation. He managed all the lab supplies and expenditures. He was also a great resource for anything in Ann Arbor. Once, I wanted marionettes for my daughters, and he knew just where to get them. He was also a regular all-around good guy, and we got to know him and his wife well over the years. He moved with us when we later relocated to Boston, and he worked for me until 2013 when he retired.

Jack and I partnered in all of our research. We essentially joined laboratories. Our graduate students knew that Jack knew the anatomy, the stereotactic surgery, all the computer programs, and the statistics, and I knew the pharmacology and physiology. Partly because of my dyslexia, and partly because of Jack's photographic memory, he was the reader. He would read all the literature and then tell me about it. I was the writer. I could express my ideas more fully than Jack, who would distill a very complex idea into an obscure pithy comment only to find it hard to elaborate. I would draft the papers and grants, and he would reference them. He did all the anatomical figures, and I did the graphs and diagrams.

We partnered clinically as well. Although we had no formal training in movement disorders, we co-directed the U of M's Movement Disorders Clinic. Sid let us hang up our shingle and say we were experts. There was no competition in Ann Arbor. We should not underestimate learning by doing. We made mistakes, but I still do today. What we learned from our patients, our basic research, and Jack's reading soon made us actual experts. Our lack of formal training meant we had fewer preconceptions about the field, so our imaginations were able to run freely.

Although we both saw a bit of everything, Jack became the expert in hypokinetic movement disorders such as Parkinson's disease, and I focused on hyperkinetic movement disorders such as Huntington's disease and Tourette's syndrome. Jack joined the local Parkinson's support group and I joined the local Huntington's disease chapter. We ran a resident and fellow Movement Disorder Clinic, and we each had a private practice clinic.

James Neel had been head of human genetics at Michigan and had canvassed the state in the 1950s to identify Huntington's disease and its prevalence. He wrote many of the classic papers on the genetics and epidemiology of Huntington's disease. As a consequence of his work, the neurology department was responsible for caring for a large number of HD patients and their families. I had the opportunity to take over the HD clinic when the neurologist caring for them left Michigan to go to the Mayo Clinic. I found it very rewarding to care for and interact with the HD families and affected individuals.

We noted that other researchers were looking at postmortem human brain neurochemistry, but they could not look at the neural circuits easily because they had to homogenize the brains to look at the neurochemicals. We decided to do autoradiography of receptors in sections of postmortem human brain. Many receptors were known or suspected to up- and down-regulate in response to under- and overactive input, respectively. Therefore, we could get some idea about how certain circuits were working by looking at receptor numbers. Jack became adept at taking 50-micron frozen sections of an entire hemisphere of human brain, and our laboratory used these to measure GABA, glutamate, dopamine, and other receptors. It was in these brains that we first saw alterations in GABA and glutamate receptors in the basal ganglia in Huntington's disease and also cortical glutamate receptors in Alzheimer's disease. When we saw something in human brain, we could take it to the animal and vice versa.

We were fortunate to have my first MD/PhD student work in the laboratory, John Timothy Greenamyre. Jack and I had been instrumental in defining glutamate as the transmitter of the corticospinal tract, and Tim was the first to measure [3H]glutamate binding autoradiographically in a rat brain. He then measured [3H]glutamate binding in HD and Alzheimer's brains. He developed autoradiographic techniques to measure all the subtypes of glutamate receptors defined physiologically. Glutamate was achieving great general interest. What had been a limited field absolutely exploded, and we were able to ride the wave at the forefront of the field. Other wonderful people to earn their PhDs in our laboratory were Helen Pan, Jang-Ho Cha, Sharin Sakurai, Claudia Testa, James Olson, Eric Richfield, William Maragos, Anthony Kincaid, John McDonald, and Brian Ciliax.

Jack and I spent our free time talking about how the basal ganglia might work. How did the message get to the spinal cord? Why did chorea initially look so fluid and then, as one lost fine motor coordination, elements of dystonia emerged? How could you be choreic and slow at the same time? Why did Parkinson's patients walk faster and faster and find it hard to stop? Could it be that in Parkinson's disease, there is not so much as too much inhibition but rather too much excitation? We wrote our theory in a review in the *Annual Review of Neuroscience*.

We decided to see what happened to GABA receptors in various parts of the basal ganglia circuit when we made lesions to different nodes of the

circuit. We predicted that if a node became underactive, postsynaptic receptors in its projection zone would upregulate; whereas if a node became overactive, postsynaptic receptors would downregulate. We did the experiments in rodents. Helen Pan, a graduate student in the laboratory, spearheaded the work. We started with the striatum. Lesions caused upregulation of GABA receptors in globus pallidus, entopeduncular nucleus, and substantia nigra pars reticulata. Receptors were downregulated in VL thalamus through trans-synaptic changes in activity. When we lesioned the cerebral cortex, GABA receptors upregulated in globus pallidus but were unchanged in entopeducular nucleus and SNr, which did not fit the simple circuit model we initially envisioned. Then, we lesioned the SNc dopamine cells, and receptors dramatically downregulated in globus pallidus and upregulated in entopeduncular nucleus and SNr. The simple circuit we hypothesized was clearly wrong.

The best explanation came from concluding that dopamine inhibited striatal GABAergic cells projecting to the globus pallidus and excited striatal GABAergic cells projecting to the entopeduncular nucleus and SNr. That only made sense if there were two circuits involved and the subthalamic nucleus was part of the second circuit. For the model to explain most of our findings, the subthalamic nucleus had to be excitatory. The current thought by others was that it was inhibitory. What *was* its neurotransmitter? Experiments by others had excluded all the monoamines, the peptide neurotransmitters, and acetylcholine. The most likely neurotransmitter was an amino acid.

Roger Albin, MD, was a postdoctoral fellow in the lab who took on the problem of the circuits with a vengeance. First, he looked at the subthalamic nucleus. We were able to obtain antibodies to glutamate, glycine, and GABA. We showed that only the anti-glutamate antibody stained the neurons in cat subthalamic nucleus. Other researchers followed shortly, and their data showed the same thing.

Our data on dopamine's differential effects on GABAergic output to the striatal projection zones also made sense with data from other labs showing that dopamine inhibited encephalin striatal turnover and enhanced substance P striatal turnover. Furthermore, others had found that substance P was present in about half of striatal neurons and encephalin in the other half. Finally, electrophysiologists had long provided evidence that application of dopamine onto medium spiny neurons of the striatum could be either excitatory or inhibitory. We hypothesized that, taken together, the data suggested that dopamine was excitatory on striatal cells projecting to the entopeduncular nucleus (medial globus pallidus in the human) and substantia nigra pars reticulata and inhibitory on striatal cells projecting to the globus pallidus (lateral globus pallidus in the human). The pathway through the cortex to striatum to entopeducular nucleus and substantia nigra pars reticulata could reinforce movements. The pathway from cortex to striatum to globus pallidus to subthalamic nucleus to entopeduncular nucleus could

inhibit unwanted movements. We published our theory in 1986 in *Movement Disorders*. The model predicted that in Huntington's disease, the striatal encephalin neurons projecting to the lateral globus pallidus would drop out first before the substance P striatal neurons projecting to medial globus pallidus and to substantia nigra pars reticulata. Second, the model predicted that the subthalamic nucleus and medial globus pallidus would be overactive in Parkinson's disease.

Roger wanted to delve deeper into the problem. He set up a collaboration with Anton Reiner, PhD, from the anatomy department, who was a good immunochemist and who wanted to get more experience in human brain. Anton's prior work as a comparative anatomist was with birds and turtles. Soon, however, we had data on substance P and encephalin immunoreactivity in Huntington's disease brains and in postmortem controls. As we had hypothesized, the encephalin neurons dropped out early and the substance P later.

Our theory that two circuits controlled basal ganglia output was new, and now we had to see if it also explained other researchers' discoveries. Mahlon DeLong and colleagues, and Michel Filion and colleagues, both were studying basal ganglia output in normal and parkinsonian monkeys. They noted the differential increase in internal and external pallidal output but were not sure how this could be understood in underlying pathways. We met and talked to them at a meeting in Manchester, England, in 1986. When Filion was presenting his work, I leaned over to DeLong and asked him if he knew how the circuits explained the findings, and he said no. I told him how our theory would explain his and Filion's work. We elaborated our thoughts in a chapter we wrote for the meeting in 1988.

Most people worked on Parkinson's disease to examine the basal ganglia, but Jack and I studied Huntington's brains as well. Our considering Parkinson's and Huntington's diseases together told us a great deal about the circuits that were affected the earliest in both diseases. In early Huntington's, the striatal encephalin neurons were affected earliest. We were able to show this in postmortem human brain from symptomatic persons and also in the brain of a presymptomatic individual whom we had seen. This latter person had committed suicide with intravenous potassium because of fear of HD. We obtained two other brains from people with early Huntington's disease who had committed suicide. One of them was a patient of mine whom I had hospitalized because of depression and whom a judge let out prematurely. The patient and her sister committed suicide together a day later.

My patients' double suicide threw me into a depression that lasted for months and disrupted my family life. Even the most beautiful days were bleak, and I was despondent and irritable. I knew how it had affected my whole family when my daughter's preschool teacher called me up and told me that my daughter had done show-and-tell on Huntington's disease and

suicide. Nancy Wexler came to my family's and my rescue psychologically, but it was a very tragic experience for me. (Nancy had become a very good friend on our trips to Venezuela—see later in this chapter.)

Devastating as those suicides were for so many people, the fact that we obtained the brains of all three victims was incredibly valuable for research. The first patient was mine and had moderate HD, her sister had very early HD, and the third person was part of a longitudinal study of at-risk sibships who had been examined two years previously with positron emission tomography (PET) scanning, psychological testing, and neurological examination. All of the at-risk person's studies had been normal, but the brain, like the two symptomatic patients, showed upregulation of GABA receptors in external globus pallidus, loss of encephalin neurons, and little loss of substance P neurons.

Roger, Jack, and I sat down to describe a new way of thinking about how the basal ganglia regulated movement in health and disease. We made a new set of box and line drawings of the circuits underlying Parkinson's and Huntington's disease. In 1989, we published it in *Trends in Neuroscience*. It turned out to be the most cited paper I have ever written. Despite huge amounts of subsequent work on the basal ganglia, our basic model has stood the test of time, and people still refer to it.

## Venezuela

A most notable part of my life and Jack's began in 1981 when Nancy Wexler invited me to participate in the Venezuela Huntington's disease project. We barely knew each other. I had met her several times casually—once at the Society for Neuroscience meetings, once when she was in Ann Arbor checking me out for the Michigan chapter of the Huntington's organization, and once at a meeting in Los Angeles for the Hereditary Disease Foundation (her father's foundation for HD). She was a strikingly beautiful woman with long blond hair, and she captivated all who were around her. Nancy had already been to Venezuela, and she was planning who would be on the team. She asked me to come along as the neurologist. We would have to go down to remote towns on stilts in lagoons along Lake Maracaibo and spend several days in the towns examining the cluster of HD patients. How exotic, I thought. I questioned my ability to function effectively in a remote environment. I decided that if Nancy could do it, so could I. I thought of hearing from Dick Johnson about his trips to Papua New Guinea to study kuru.

This trip with Nancy began 22 years of returning to Venezuela each year to study the very large HD family that exists there along the shores of Lake Maracaibo. Huntington's disease first appeared there in the 1800s. Whether it was a new mutation or from an itinerant sailor is still unknown. Over the 22-year period, I saw thousands of people at risk for and with HD, some homozygous for the gene. For some people, we had up to 22 years of

follow-up exams, with videos. After the second year of the study, Jack also began to take part in the trips. The two of us would go down at different times because we always wanted one parent at home. On a couple of occasions, the kids came down with us, and then we could all be together. Jack helped create a neurology database. Jack and I competed to see how many people we could examine each year.

Jack and I viewed our time in Venezuela as soldiers in the field. Many personal events took place during those 22 years of trips, including developing very strong and lasting friendships, mentoring young people, being held up by armed guards, and nearly dying when our boat began to sink during a storm. Despite the dangers, we all made it through unscathed. Our experiences gave us a much deeper sense about the challenges faced by the populations of the underdeveloped world.

Nancy Wexler proved to be the most hardworking, driven person imaginable (Figure 1). She taught herself Spanish so she could communicate effectively. She knew the pedigree inside out and backward. She knew the names and relatives of nearly everybody. She would listen to their stories and cajole them to participate in the study. Her blond hair flowing, she would walk through towns and neighborhoods, stopping at houses where

**Fig. 1.** Nancy Wexler with children in Venezuela.

an HD family lived and soon 10–20 people would arrive who were part of the family. They called her *La Catira* or "The Blond." Nearly all volunteered, and Nancy would explain that her own mother had HD and so she knew how they all felt about the disease. Nancy would not hesitate to get in close to people despite the conditions. She hugged everyone, particularly the affected people. She went into their homes, attended to their troubles, asked about their families, and helped them get everything from medicines to mattresses. Nancy made the most of every waking hour—and for her, three to four hours of sleep was enough. We would be up at dawn and then work until 10 p.m. or 2 a.m. During trips on trucks or buses, we could sometimes catch a few winks.

In Venezuela, we all became adept at drawing blood, taking skin biopsies, doing neuro exams, and at videotaping exams. We persuaded the Venezuelan men to give sperm samples as well. We brought the samples and data we obtained back to the United States and distributed them to other laboratories. The samples became an important resource for many lab groups.

In 1983, two years into the Venezuela project, the samples helped find a marker that was closely linked to the Huntington's gene. Jim Gusella, at Massachusetts General Hospital, found it by using immortalized lymphocytes from Venezuelan blood samples. Jim had come from David Housman's lab at Massachusetts Institute of Technology (MIT) to Mass General, and David had been the one to conceive of screening the human genome with anonymous RFLP markers in a large family to find the gene. Jim was going to set up the experiment in a new HD center at Mass General run by Joseph Martin, who was head of the neurology service there. Nancy's father's organization, the Hereditary Disease Foundation, helped fund the project as did the National Institutes of Health (NIH). The discovery of the HD gene marker allowed the use of linkage analysis to determine who had inherited the HD gene. People who had living affected family members could have linkage analysis to determine presymptomatically whether they had inherited the mutant gene.

Geneticists in the United States and abroad mounted a huge effort to find the actual gene. The hunt depended in part on getting more genetic data from the pedigree. More cases could narrow the area in which the gene could reside. We worked furiously in Venezuela. Each year, Nancy would tell me that I had to see several people myself to see if they had HD. She told me that my exams were the gold standard. I was totally blind to the genotyping being done for the pedigree but clearly either somebody was "diagnosed" who should not have been (i.e., misdiagnosed) or else they had HD but had not been diagnosed yet. As before, I just did as Nancy said. I put down my opinion, and we would not talk about it further.

Nancy thought broadly. She recruited geneticists who brought yeast, flies, and worms to the hunt because they used different techniques than

human geneticists to work with DNA. All the methods proved useful when narrowing the site for the mutation on chromosome 4. Nancy brought the team together several times a year to exchange data and to discuss the next steps.

## Recruitment to Mass General

At Michigan, I was fortunate that our research went well and I was getting grants. I was promoted to associate professor and then full professor by the time I was 38. I put together a proposal for an Alzheimer's Disease Research Center at Michigan, and it was awarded. I had to run the center, and I was doing other administrative work also. At that point, I began getting letters asking if I was interested in becoming chair of a department or a director of a program with an endowed professorship. I knew the requests came mostly because I was a woman and they needed women candidates. I looked at only a couple of positions because I loved my job at Michigan. Then one day I got a letter from Massachusetts General Hospital (MGH) asking if I would be a candidate for the position of their chief of neurology. This was the job that Joseph Martin had just left to become dean at UCSF. This was one of the all-time premier departments in the country and clearly the place to be if you were interested in HD.

I decided to look at the job. Jack did not think it would amount to anything, but his family was in Boston so he did not object. The first visit was memorable. I had very long hair that I wore in a ponytail on one side. I did not have any suits, so I wore a fairly casual dress. I had breakfast with the chair of the search committee, John Potts, the chief of medicine. He told me how much fun MGH was, and how you could have a vision and really carry it through at this institution. The rest of the day I saw all men, the whole search committee. I would see one person and then go to the lobby of another building to wait for the secretary of the next person. Because I did not look like the candidates they were used to, the secretaries never found me; I found the secretaries. The whole process seemed like an affirmative action pretense at being interested in a woman candidate, so I figured I did not have a chance. Therefore, I was completely blunt when I described my vision for the department in my final session with the search committee. I was shocked when I was asked back to MGH for a second look, and even more shocked when, in September 1990, John Potts called to actually offer me the job.

Then came the haggling over the agreement. I received help negotiating from Herb Pardes, Nancy's partner. He told me to negotiate like Peter Falk in "Columbo." Simply scratch your head and think out loud about how you cannot possibly make it the best department there is without so many new recruits, so much more for infrastructure support, and without funds for so many more fellows. I had never negotiated before, but I did my homework

and asked for a lot. Nancy's father, Milton Wexler, gave me a great piece of advice about how to decide whether to go to MGH or to stay at Michigan. He said that I should simply negotiate until it clearly felt good to go to MGH. If it ever got that far then I should go, but if it did not, I should stay at Michigan. Sid wanted me to stay but the one thing I wanted—an endowed chair—he did not have to offer me. Jack did not want to go at first because he had all his patients and also a very nice position as professor. I negotiated for a nice laboratory for us, a professor position for Jack at Harvard and MGH, and an instructor position for my laboratory manager, Zane Hollingsworth. The rest of the negotiations were for new positions in several undermanned areas and for fellows for many of the staff who were trying to do everything with little help and no infrastructure. I thought that the strengths for the department could be vastly enhanced by junior help for the more senior people. Eventually, I got everything I asked for, and I accepted.

I was the first woman chair of a department at MGH. When I arrived, I felt comfortable until someone leaned over and said: "Do you feel comfortable here?" Truthfully, I was always treated very nicely at MGH, but I was never part of the inner circle.

Nonetheless, I was able to get things done. One of my residents later told me that she had been told by another professor that I would probably be eaten alive by the old boys who ran MGH. The same professor told her a few years later that he had been completely wrong—that I had pushed through a change from a private inpatient service to a ward service that no previous chairman had been able to accomplish.

Moving the girls was a challenge. One wanted to go, and the other definitely did not. They had a series of demands themselves, so I had to negotiate with them as well as with MGH. One of their demands was a house with a yard where they could play. They were not being very forward thinking about that because, as it turned out, they became adolescents at just about the time of the move. I do not think they ever played in the yard; instead, they adapted themselves to their new lives as teenagers. We left Joan the babysitter behind in Ann Arbor, after living with her for 14 years. The girls were old enough to watch over themselves and Joan, by that point, had a significant other. She moved in with him as soon as we left. She later had two sons.

I started my new job at MGH on August 1, 1991. Zane took on the cumbersome job of moving the lab. His organization was outstanding, and we were up and working in no time. We helped most of our graduate students finish up and arrived in Boston with one graduate student, one technician, and two fellows (Leon Dure and Mara Catania). David Standaert joined the lab (as a fellow) just as we were starting up at MGH.

At that time, we were particularly interested in defining the receptor phenotypes of striatal neurons. We thought that differential cell death in illnesses such as Huntington's disease could stem from the differential

expression of different subtypes of NMDA, AMPA, and kainate receptors. We combined radioactive and immunochemical methods of measuring mRNA of various transmitter subtypes. The methods were challenging, but we perfected them in the lab. Postdoctoral fellows David Standaert, Bernhardt Landwehrmeyer, Christoph Kosinski, Ulrich Wullner, Clemens Scherzer, Josef Priller, and others all contributed important efforts into these studies.

One of the challenges for me was finding a good secretary. Unfortunately, the secretaries who came with the job were slow, passive aggressive, and prejudiced. I caught them being nice to all the Christians but rude and unfriendly to Jews and foreigners. I had to fire all of them. That instantly gave me the reputation as a bitch, and I could not find another secretary who would even apply for the job.

Finally, a woman named Beverly Mahfuz applied. Clearly, Bev was very smart. She said she was a fast reader and could read all my mail and summarize it for me. I hired her right away. She is wonderful, and we continue to work together to this day 21 years later!!! Bev has made my life much, much easier. The two of us work together almost seamlessly. Bev is my right hand. She is definitely the power behind my facade for the whole department. Eventually, she knew more about what people needed for promotions than anyone else, and she became an excellent advisor for junior faculty moving up the ladder. She not only reads my mail, she can read me like a book, and she knows how to make the same kind of decisions that I do. She also knows the people at all levels of the hospital so that if something needs to be done, she knows whom to call to make it happen.

Just two years into my tenure as chief, two important papers came out of MGH in the same month—March 1993. One reported the identification of the HD gene. Jim Gusella and Marcy Macdonald played key roles in the discovery. The second paper by Robert Brown and his group at MGH, identified the gene mutation in SOD1 (superoxide dismutase, type 1) that leads to some forms of familial amyotrophic lateral sclerosis (ALS). I was immensely proud of our department, although I knew I could not take credit for this good work. My predecessor Joe Martin's efforts to put neurogenetics on the map at MGH had finally paid off on my watch.

The other illness receiving a great deal of attention in our department as well as nationally was Alzheimer's disease (AD). Jim Gusella, Rudy Tanzi, and MGH were key in identifying the amyloid precursor protein gene and subsequently mutations in the presenilin gene. These genetic discoveries in HD, ALS, and AD (all made possible in part by the DNA from the Venezuelan HD family) set the stage worldwide for the next 10 years or more of mapping the human genome, collecting families with a variety of nervous system disorders.

After the discovery of the HD gene, the next few years of scientific advances were slow. A very wealthy donor, along with Nancy Wexler, David Housman, Richard Mulligan, Robert Horwitz, and I, began an effort to push

toward a cure faster. We began a series of regular meetings at MIT to discuss important avenues of research that should be funded. We often targeted a particular investigator based on his or her known scientific skills and asked them to become involved in HD research. The donor was extremely wealthy and funded all our efforts. The targeting brought in many new scientists to the HD field. The Hereditary Disease Foundation (which Nancy's father Milton had started in the 1960s and of which Nancy had assumed leadership) began a series of August meetings every other year in Boston to bring together HD researchers. Data blitzes were the highlight of the meetings because people would have five to seven minutes to tell only their latest results. Posters also became a vehicle for communication. These meetings continue to this day, and the numbers of researchers has expanded dramatically.

The donor eventually decided to form his own virtual nonprofit company to fund HD research. The Hereditary Disease Foundation continues to do well and funds key high risk–high payoff research and fellowships and conducts workshops on cutting-edge research. Work on HD continues unabated, and many new and exciting experiments have implications for patients, particularly gene silencing methods.

## The Huntington's Study Group

In 1993, after the Huntington's genetic mutation was identified, long-time colleague and collaborator, Ira Shoulson, got together with Jack and decided to start the "Huntington's Study Group" (HSG). This group was the final piece of the HD pie. The idea was to form a multicenter group that could mount clinical trials quickly and efficiently. Ira and Jack were co-directors of the HSG, and I was head of the scientific advisory committee of the HSG. To be part of the group, investigators had to agree to use common measurement scales of motor, cognitive, and behavioral function. Each site had to train investigators in the use of the scales. Protocols for drug studies were shared among the HSG sites. The HSG not only contracted with drug companies to do studies but also wrote grants to the NIH to fund observational and intervention studies. The HSG continues to this day and has run studies on the natural history of HD and on the efficacy of multiple drugs for HD including tetrabenazine, which is currently the only drug specifically marketed for the chorea of HD.

Jack and Ira became fast friends. Jack was a quiet man, but with Ira, he functioned as a solid and reliable sounding board. Jack was very ethical, which made him an excellent advisor when it came to conflict of interest or other organizational and scientific issues. Jack was also excellent at data analysis and worked closely with David Oakes, the statistician for the HSG. They would go over the large data sets from HSG studies and come up with observations about the natural history and the effects of certain agents on HD (Figure 2).

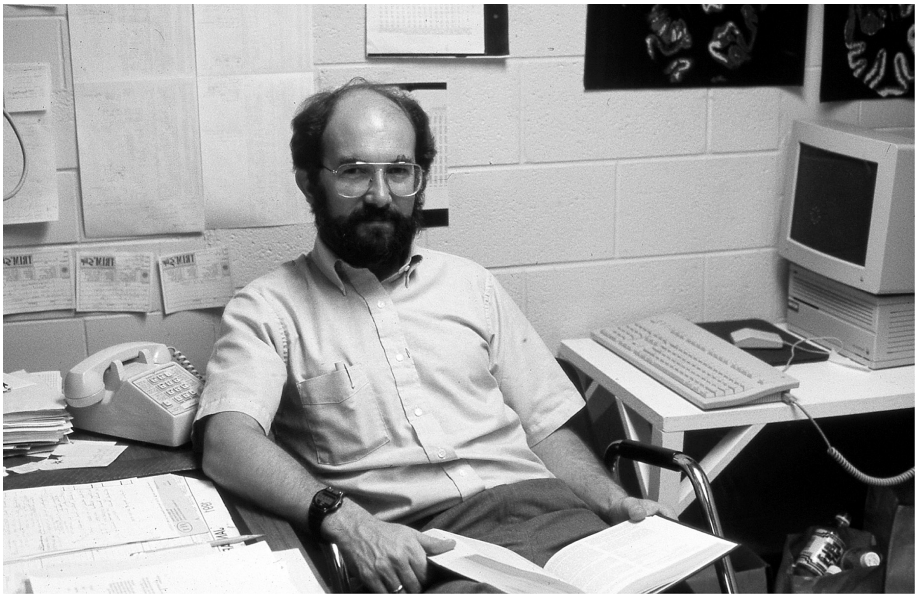

**Fig. 2.** Jack Penney.

## Women in Academic Medicine

As chief of the neurology service at MGH, I learned a great deal about men and women in academic medicine. The most important observation was that men had no hesitation asking for the moon from the chief, whereas the women rarely asked for anything. This observation was even true for women who were aggressive when it came to patient care or research. When it came to asking for themselves, it would not happen. I had to train the women in the department to stick up for themselves and to ask for resources and space when they needed it. Merit Cudkowicz (now chief of MGH neurology) was the first woman to ask me outright for a raise. Diana Rosas, Karen Furie, Natalia Rost, and Nicte Mejia have all benefited from my mentorship and have learned to negotiate appropriately.

The second most important thing I learned was that at least part of the challenge in getting women promoted was not that the leadership was bad per se. Rather, women either never got on or promptly fell off the radar screen of leadership because they would not complain or ask for things. Women were not in any inner circles of their departments. Promoting women at the medical school was not difficult once the department showed interest and support. Recognizing their accomplishments took active surveillance, however.

The third aspect of women in neurology was that having role models was very important for the young women coming into residency. They could join an inner circle of strong women who would teach them the ropes if they did not feel comfortable working in a man's world.

Finally, more women than men choose to limit their academic efforts in favor of spending more time with their families. Fortunately for those of us in the clinical departments, there is no clock for promotions at the medical school. That means that women can take more time to get promoted without being penalized for spending more time with their families during critical times of their careers.

## Partners Neurology

In 1994, MGH and Brigham and Women's Hospital (BWH) decided to join forces in the health care arena and form Partners HealthCare. Suddenly, two rival hospitals were joined at the hip. Neurology was not a department at BWH, and so I lobbied that it become one so that our departments could partner together instead of compete. This was a foreign concept to the other chiefs. In the spirit of partnership, neurology was made a department at BWH. Martin Samuels became chief of neurology at BWH. He was known for his skills as a teacher and as a clinician. Together, Marty and I arranged for the longstanding Longwood Neurology Training Program to be dissolved and reconfigured such that the Beth Israel and Children's would become independent and BWH would join in a Partners Neurology training program with the longstanding independent MGH program. The first class entered in 1996.

Our collaborative efforts allowed the MGH neurology department to apply for funding directly from the new Partners HealthCare. We got funding for an administrator, an access nurse, a residency coordinator, and funds to support technologies to assist the residents at the two hospitals. We began having joint faculty meetings so that people would get to know each other. Initially, we did not set up rival clinical programs so as not to compete for patients. MGH was strong in movement disorders and neurodegenerative diseases whereas BWH was strong in neuroimmunology. Marty and I decided that patients with multiple sclerosis would be seen at BWH and movement disorders would be seen at MGH. A limited number of faculty worked at both institutions. This division of labor was partly successful, but there were many patients who only wanted care at one institution. This eventually resulted in the need for limited neuroimmunology and movement disorders at both institutions.

During this time, our laboratory continued to focus on studies of various glutamate receptors in rodent and human brains. We found several areas of unique receptor distribution, and these have subsequently been found to have potential pharmacologic specificity in targeting certain clinical

symptoms and behavioral effects. We also collaborated with Jim Gusella and Marcy MacDonald and examined the distribution of HD mRNA in human and rodent brains. Predominantly, though, we focused on glutamate receptors in rodent basal ganglia.

In 1998, mutations in alpha-synuclein were identified in familial PD. Jack figured that the expertise in our lab could be put to good use in studying PD and wrote a program project grant that included our lab and the labs of Ann Graybiel, Brad Hyman, and Xandra Breakefield. The grant was for a Udall Center for Excellence in Parkinson's Research. Jack got the grant, and the center started in the fall of 1998. The MGH-MIT Morris Udall Center for Excellence in PD Research had the overall theme of understanding the mechanisms by which abnormalities in synuclein, parkin, torsinA, and related proteins lead to dopamine cell dysfunction and neurodegeneration. The center encompassed four projects: an *in situ* hybridization-based investigation into gene expression and selective vulnerability in Parkinson's disease substantia nigra, led by the principal investigator (P.I.), Dr. Jack Penney. Dr. Hyman explored the expression of alpha-synuclein using then new fluorescence energy transfer techniques to examine its location in cells *in vitro*. Dr. Breakefield investigated the genetics of parkinsonism, dystonia, and rapid onset parkinsonism-dystonia with an emphasis on her studies of torsinA. Dr. Graybiel developed more sophisticated electrophysiologic approaches to studying the role of basal ganglia in learning and movement using tetrode arrays in mice and rats during acquisitions of novel behaviors. She also pursued experiments using changes in immediate early gene expression to assess the circuits involved in motor learning and adaptation following dopamine agonist treatment.

## Creating the MassGeneral Institute for Neurodegenerative Diseases

Over the years, I had become convinced that in most drug companies, development of new treatments centered on compounds that had been discovered years before. To get modern discoveries more quickly to people, investigators needed to have the resources to set up an assay and to do high throughput screening for potential therapeutic candidates right there in the academic laboratory, rather than waiting for years before the drug company would consider them. To get compounds for proof of principle experiments and subsequently for partnering with industry, Jack and I thought that if we could put all the people working on neurodegenerative disease at MGH together in one place, and add a drug screening lab to the mix, we would have a unique center and a real powerhouse. All we needed was a building.

I was on a space committee, and I heard about an old Navy building in the Charlestown Navy Yard that had been gutted by fire but that was up for sale. The building was close to an already existing MGH research building.

I asked my friends if any proposals for use of the space had been made, and the answer was "no." I immediately put forward a plan to have it house an MGH Center for Aging, Genetics and Neurodegeneration (CAGN, or CAGn with its connection to Huntington's disease). I wanted the whole building. It would have open laboratories, good communication between floors, and a collaborative atmosphere. I found a donor who was willing to give $2 million to help get it started; $2 million was not enough to rebuild the building—that would take much more. Therefore, the hospital administrators had to decide whether to invest in my vision. They liked my plan, in part because I proposed to free up other space they could then give to key researchers in other departments. It was to be win-win for a lot of people.

All was going well in the negotiations, but I had to present to several committees before any decision was made. A key presentation kept me from going to the Winter Brain Research meeting in Aspen that January 1999. Instead Jack went with my younger daughter, Ellen, who was then age 19. My presentation went well. The hospital administration approved my plan and said I could have two-thirds of the building. A coup! Although the whole building was my dream, two-thirds was more than enough space for us and would allow all the planned programs to go into the building.

That evening I called Jack to tell him. He was ecstatic. A few days later, he and Ellen returned after a day of skiing at the end of the conference. That night as we lay in bed, Jack suddenly gave a large gasp. And died. I gave him CPR for what seemed like hours until the ambulance came but with each chest compression I knew it was hopeless. A massive heart attack. He was just 51.

Nothing in my life could have been worse. Jack and I were together in every aspect of our lives. He was my husband and my best friend, my co-resident, my most important research collaborator. He told me when it was time to go home from a party and what was important in the latest journals. Every aspect of my life was instantly crushed. Even now, 14 years later, it is raw and bitter. Thank God for all my friends. Nancy was by my side in what seemed like just minutes, Zane, Jang-Ho, Sharin Sakurai, Alice Flaherty, and Diana Rosas were there quickly also. Jim Olson from Seattle came and spent a week trying to help. My daughter Ellen, who had had to watch me try hopelessly to revive Jack was with me too as was Jessica (our oldest daughter) who flew in immediately from Michigan. Our apartment was within walking distance of the hospital, and nearly everyone in the department came by and stayed for hours. For 12 days, my apartment was full of people and constant noise.

Remarkably, in the days following Jack's death, several of my trainees decided to collaborate on new projects. In particular, Jim Olson, a pediatric neuro-oncologist, worked out a collaboration in my laboratory on gene expression studies in HD with Ruth Luthi-Carter. Jim was an expert from an oncology background and Ruth was a good molecular biologist. Jang-Ho Cha, a contemporary of Jim's in the lab from Michigan joined the

collaboration, too. Jang-Ho had done his neurology training at MGH and then worked in my lab again. (Jang-Ho had previously observed that in HD transgenic mice, neurotransmitter receptors were changed in a pattern that suggested altered gene transcription of certain receptors but not others.) This began the first gene expression studies in HD animal models and in the HD brain. It was found that in HD there are remarkable changes in subsets of genes suggesting that the mutant protein alters specific gene expression via altering transcription.

Because Jack ran through every aspect of my life, there was nowhere to go to escape the intense grief. His absence was everywhere. I had to take over direction of the Udall Center and write grant renewals that Jack had been working on. For the next two years, my students and colleagues all rallied around to help me through the most difficult time imaginable. My colleagues, particularly Jang-Ho Cha and David Standaert, helped write grant renewals that got funded.

I tried to channel my efforts into the new Center for Aging, Genetics and Neurodegeneration, the last project that Jack and I had started together. Three weeks after Jack's death, I had one final hurdle to go through in front of the finance committee at Partners HealthCare to sell the idea and convince the committee to buy and renovate the new building. I dressed all in black and made a passionate plea based on my late husband's and my concept for a center that could focus on accelerating new therapies for neurodegenerative disease by bringing fundamental discoveries more quickly to application. Although by no means unanimous, the motion passed and soon we began designing the center.

The center opened up lab space for Brad Hyman, Rudy Tanzi, David Standaert, Marian DiFiglia, Jang-Ho Cha, and Bob Brown and a host of more junior people. We had 36,000 square feet of prime research space on two floors with an open staircase that connected the two floors. The $2 million helped get people set up, to hire a person to be the executive director, and helped fundraise and maintain center infrastructure. I hired Janice Hayes Cha, Jang-Ho's wife, to fill the position. She is the type of person who is self-motivated and just knows how to get things done. Zane was designated the center manager who coordinated the space moves and kept me abreast of space wars that existed between investigators. Each year, Janice brought in philanthropic support that allowed us to do the drug screening, to support young people, and to get new equipment. One of the donors said our name was too confusing and we should rename the center. We chose the MassGeneral Institute for Neurodegenerative Diseases (MIND).

Just as MIND was getting off the ground, I sent a summary of my plan to Dennis Selkoe over at BWH. Shortly after this happened, a large anonymous $37 million gift was made to Harvard Medical School with Dennis Selkoe and Joe Martin (who had returned from UCSF to become dean at Harvard Medical School) as the leaders to set up an almost identical center at the medical school. They had drug screening, fellowships, grants, and

so on. They collaborated with us and one of their core facilities (the laser capture microdissection core) is at MIND. It was a center without walls, so there was no building for it. Many people around the medical school were part of it including many of our investigators.

## Novartis Collaboration

Shortly after MIND opened, David Housman from MIT and I decided to approach Novartis for a collaborative effort to solve Huntington's disease. Two of David's prior postdocs had junior faculty positions in MIND and one, Alex Kazantsev, was the head of the drug screening lab. Alex had found an interesting compound that seemed to block aggregation of proteins in HD. At MIND, he looked at analogs of the compound and found one that was very effective and potent. Novartis looked at the compound and found that it was orally bioavailable and was nontoxic.

In 2006, we put together a four-year, multi-lab project with Novartis to uncover agents to treat HD. The project supported five postdocs plus money for supplies and animal experiments at MGH and MIT, and Novartis contributed considerable resources on their side as well. The projects were to follow up on Alex's drug and find agents that effected (1) huntingtin proteolysis, (2) huntingtin-induced abnormal transcription, and (3) huntingtin clearance.

The Novartis neuroscience team was located primarily in Basel, Switzerland, with a few people in Cambridge, Mass. The distance and the difficulty getting things in a timely fashion made the collaboration challenging. Although we did not find any drugs that altered HD gene transcription, we did find drugs that altered the proteasome breakdown of huntingtin. We also advanced the field by coming up with a good assay for the huntingtin protein. We looked hard for drugs that could simply lower HTT expression, but we found none. The one drug we found that had worked in aggregation and had the potent IC50 was not taken up by Novartis. After four years, the contract was not renewed; shortly thereafter, Novartis closed its neuroscience division. We are still working on our drug, and Alex has a grant from NIH to try to develop it to the point of an IND. Our experience with Novartis was a good one and all the investigators have stayed friends. It taught us however about the vast difference between being an investigator in a drug company and being an investigator in academics.

## American Neurological Association

The American Neurological Association (ANA) is the oldest neurological association in the country, and its members have always been chosen by a membership committee that scrutinizes the individual's academic contributions and then the membership votes on the candidates. Typically, people were not admitted before they attained the academic rank of associate professor. The ANA is comprised exclusively of academic neurologists.

In 2001, two years after Jack's death, I was elected president of the ANA— the second woman to have held that position. It was a great honor and the work was fun not onerous. I held the position for two years, and during that time we had a wonderful meeting in New York and another in San Francisco. During the time of my presidency, a mentoring program for neurologists and neurosurgeons was developed by joint efforts of the ANA and NINDS. This one-and-a-half-day program still takes place on the day before the official onset of the annual ANA meeting. We also began a discussion about opening up the membership to a broader and younger group of academic neurologists.

## Society for Neuroscience

In 2003, I was elected president of the Society for Neuroscience (SfN). I should have had a year as president-elect, but Story Landis who was in line to be president had to bow out because of her position at NIH. I stepped directly into the position of president. At the time, the SfN had made a decision to build a building for their organization in Washington, D.C. During my watch, we had to design the building. We decided to go for the top designation of environmentally friendly architecture. We chose all the materials for the various spaces as well as the lighting to keep the spaces open and friendly. It was a fun project and the resultant building is extremely cost-effective.

I made neurodegenerative disease my theme for the meeting when I was president. I had a presidential symposium featuring lead researchers in four prominent neurodegenerative diseases: Alzheimer's disease, Parkinson's disease, Huntington's disease, and Lou Gehrig's disease (ALS). I had short, five-minute videos made introducing the clinical aspects of disease for the audience of basic neuroscientists. Everybody at the meeting could then get a copy of the videos for their use in classes back at their institutions.

The added bonus to my year as president was that the Boston Red Sox were in the World Series that year and on one of the nights at the meeting in San Diego, the Red Sox played their final game. We had a big party up in the presidential suite and watched them win the championship!

## Getting My Life Back Together

In 2005, I received an e-mail from Stetson Ames, a high school boyfriend who I had not seen in 35 years. I was busy and I did not answer back for a month. Once I did, we reconnected easily. It was as if no time had passed. I invited him out for a visit, and because he was retired from his career in law enforcement, he was able to come. His wife had passed away as well. We hit it off and soon got married. He had spent his summers near Boston as a child and so he liked the idea of moving there. He is completely different from Jack, so I do not spend any time comparing the two. Stets was completely comfortable with me as head of a department. Because he knew

me from childhood, I could not expect any special treatment. On the other hand, because I am still working, he is very tolerant and takes good care of me.

My oldest daughter, Jessica, teaches science and math to seventh graders in Manhattan. She and her husband have a son who is now four. My other daughter, Ellen, finished an MD/PhD at Columbia University School of Medicine. She is now a resident in neurology in the Partners training program.

## MassGeneral Institute for Neurodegenerative Diseases

Collaborations within MIND grew. As researchers were successful, though, their reputations grew and other institutions recruited them away. Bob Brown became the chair of neurology at the University of Massachusetts. David Standaert was recruited to run a new similar center at the University of Alabama. Jang-Ho Cha went to Merck. Although I always regretted losing a friend and colleague, I also encouraged my junior colleagues to interview at other institutions—they owed it to their own careers to know their value elsewhere.

Many people chose to stay, however, and I worked hard to get them the best possible situations within our institutions. I got two endowed chairs funded, which I gave to Rudy Tanzi and Brad Hyman. (I then obtained funding for five additional chairs for other key faculty members in various areas of the department.) Researchers continue to find MIND to be a most stimulating place and so it has continued to thrive. Now, after 12 years, we have drugs in animal trials or in human trials for each of the neurodegenerative diseases. Furthermore, several of the agents are being tried in more than one neurodegenerative disorder—supporting the initial notion that the similarities of these diseases might lead to common mechanisms of neurodegeneration and therefore common means of treatment.

My laboratory gradually decreased in size. This was partly because the many jobs I had taken on meant that I could not really keep up with the literature. I missed having Jack to bounce ideas off. My graduate student Lianna Orlando stayed on for a postdoctoral fellowship and for a junior faculty position, and we worked together on experiments that indicated an interaction of huntingtin with mGluR5 receptors. A postdoctoral fellow of David Standaert's, Ippolita Cantuti-Castelvetri, joined the lab to work on Parkinson's disease. She had found two very interesting results. First, gene expression changes in dopamine neurons are strikingly different between men and women, and second, women seem to process alpha-synuclein differently than men. Time will tell whether this holds up in future investigations. In work with Ann Graybiel in mice with l-DOPA-induced dyskinesias, we found that thyrotropin-releasing hormone (TRH) was massively increased in the striatum and in striatal output areas in relation to the degree of dyskinesia. This becomes a new and novel target for treating dyskinesias.

## Stepping Down as Department Chair

In 2010, I notified the president of MGH, Peter Slavin, that I would like to step down as chair of neurology. I had made the mark I had wanted on my department and on my field. I left the department nearly at its peak. We were moving all our inpatients to a spectacular new building with three neurology floors including a new neuro-ICU that had its own PET scanner and magnetic resonance imaging (MRI) scanner. The department was bringing in more money than ever before, and our patient load and admissions were at an all-time high. I figured it would take a year to find my replacement and then I would have been chief for 20 years. As it was, it took two years and in May 2012, I gave up my position and my replacement, a wonderful woman from MGH, Merit Cudkowicz, took over. She was an internal candidate but by far the best. She had trained in our residency program and started the first MGH Neurology Clinical Trials Unit. She was the first woman in my department to spontaneously ask me for a raise. I was so proud of her at the time that I quickly gave her a hug.

## Post-Chief Era

The first thing I did after I stepped down as chief was to rent a boat in the Galapagos and invite all my friends for a vacation of a lifetime. Chief of these was Nancy Wexler, who has been so important to me at every stage of my life.

Since May 2012, I have given up my lab because I think younger people need the space and resources more than I do and because I would have to take a sabbatical to learn the new techniques that have been developed before really setting up my lab for the future. I decided that I would be better off giving up the lab and spending time on mentoring others. I continue to see my patients who depend on me.

In 2010, my mother died at the age of 90. I inherited more money than I expected due to the lack of taxes that year. I decided to give $1 million as a charitable annuity to MGH. It was very amusing to write a check for one million and 00/100 dollars as a personal check. That gift made me the first chief to have made such a contribution to MGH. It also brought forward the need for philanthropy in these days of limited NIH resources. I decided to become a fundraiser for the department as one of my main goals since resigning as chief. I find the job fun and rewarding because I am fundraising not for myself but for others in the department. It is very fulfilling work.

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