Interview with M. Marsel Mesulam, MD, FAAN
American Academy of Neurology
Oral History Project

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Ruth Dunbar Davee Professor of Neuroscience and
Director of the Cognitive Neurology and Alzheimer's Disease Center
Northwestern University Medical School
Chicago, Illinois

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Kirk R. Daffner, MD and
Lauren E. Klaffke, Interviewers

M. Marsel Mesulam - MM
Kirk Daffner - KD
Lauren Klaffke - LK

LK: This is Lauren Klaffke. It's January 12, 2015. I'm here today with Doctor Kirk Daffner and Doctor Marsel Mesulam at the Cognitive Neurology and Alzheimer's Disease Center at Northwestern University Medical School. Doctor Daffner and I are interviewing Doctor Mesulam for the American Academy of Neurology [AAN] Oral History Project.

Doctor Mesulam attended Harvard University for his undergraduate and medical degrees. He completed his internship at the hospital of the University of Pennsylvania and his residency at Boston City Hospital [BCH] and Beth Israel [BI] Hospital. He became a professor of neurology at Harvard Medical School and served as acting chairman of the Department of Neurology. In 1994, he moved to Northwestern University Medical School where he holds the Ruth and Evelyn Dunbar Professor of Psychiatry and Behavioral Sciences chair and, later, a joint appointment as a professor of psychology. He is director of the Cognitive Neurology and Alzheimer's Disease Center.

Thank you all for coming together today for this interview.

MM: One correction.

LK: Sure.

MM: For my professorship, the chair's name has changed. I am now the Ruth Dunbar Davee Professor of Neuroscience.

LK: Okay. On the record.

KD: To give a broad overview of the kinds of things we're going to cover… Not surprisingly, we'll start with early life and education, Harvard College, and, then, turn to years in medical school, general training, a lot of questions around Boston City Hospital and Beth Israel in terms of residency and training. We'll talk about research interests and outcomes in your time at Harvard and Beth Israel, then your time here at Northwestern. We'll talk a little about teaching and mentoring and get your general perspective on the future, so a few things.

LK: [laughter] Just a few.

To get us started, we are wondering if you could tell us about your early life and education.

MM: Sure. I was born in Istanbul [Turkey] in 1945. I have beautiful memories of Istanbul. It was a wonderful time to be living in that city even though there were challenges. I think the first ten, eleven years of my existence, there was nothing particular other than going through the usual stages of elementary school and so on, a very comfortable childhood. We lived in nice parts of the city. At that time, the city offered all kinds of things for a very small population, so we were really privileged.

Then, I went to high school. The high school's name was Robert Academy. It was established by American missionaries, I believe during the Crimean War. That's when Florence Nightingale was also establishing hospitals in Istanbul. The school had a *very* strong curriculum. I was there for many years. I had to have two years of preparatory school because I knew no English whatsoever. English was taught as a second language there. That's when I was eleven years old and so on. The world then was going through interesting phases. It was the height of the Cold War. Russia had just invaded Czechoslovakia. France and England were attacking the Suez Canal. There was interesting news as I went through high school in Robert Academy. There, really, things started to flourish. I was the editor in chief of the newspaper, their school paper [*Bosphorous Chronicle*]. Initially, when I started to work on the newspaper, it was mimeographed, so I established a more professional approach. We had it printed professionally and the newspaper continues in that form until now. I was president of the student council. I got lots of prizes, too many prizes probably. I had a wonderful time. It was a *very* strong curriculum. By the time I came to Harvard as a freshman, I was ahead of just about the whole class in terms of general information, literature, that sort of thing.

When high school came to an end, I had to make a decision. Because some of our teachers were American, they suggested applying to some American colleges. I applied to Yale, Columbia, MIT [Massachusetts Institute of Technology], and Harvard. I got into

all of them and, then, I couldn't decide what to do. I had a copy of the *Encyclopedia Britannica*, which I opened up and found that Harvard was founded first, so I accepted Harvard's offer.

KD and LK: [chuckles]

MM: I was the first Turk accepted in twenty-five years to Harvard.

Really, the academic curriculum was not difficult. I was prepared in just about every field. The beauty about Harvard is that you could obsess about what you want to do with your life. I got interested in literature, economics, physics. In fact, I wanted to be a physicist and, thank God, one of my roommates later became chairman of physics at Harvard and I immediately realized physics was not for me. I just did not have the talent. This guy could do things in thirty seconds and I would sweat over it the whole weekend. So that was out.

I don't know exactly how, but I really got interested in [Sigmund] Freud. I took a number of courses and read *a lot* of Freud, and I wanted to become a psychiatrist, especially a psychoanalyst. But, then, things started to get a little problematic because I read Freud's essay. I think it was called *Project for a Scientific Psychology* [1895], or some such thing, where, at that point, he simply says, "These are beautiful things that I have: id, egos, superegos. But biology is just not ready to tell us what happens in the brain." That, I suppose, kind of intrigued me. So the rest of my undergraduate years dealt with the mind/body problem. How does mind affect body? At that time, even simple issues then were unsettled.

I took a course in psychophysiology. It was a hands-on course. The wizard there was a man called Bernard Tursky who made important contributions to psychophysiology. I ran my own studies including one where I would hook my girlfriend up to the polygraph and ask her to think about something really exciting and, then, her GSP [galvanic skin potential] would just go sky high. I never asked her what it was that she thought about.

LK: [chuckles]

MM: I had a boa constrictor that I used in the experiment, so one of my coworkers would put the boa constrictor around her neck and we would have somebody [unclear] to the polygraph watch this and see what the reaction would be. Surprisingly, it was not that great. That was the kind of approach I had to the mind/body problem just to prove that when something happens in the mind, there was something in the body that was related to that.

That led me to my thesis for graduation and that's where, actually, Kirk comes in.

My thesis was on novelty-seeking behavior as measured by eye movements in schizophrenics. I did the study at that time in the Boston State Hospital where large numbers of schizophrenics were hospitalized. We had a polygraph there, very, very old

fashioned, still the old fashioned tubes, cathode ray tubes. Bernie Tursky was the only person who could keep it alive. We tested and we gave patients a choice between two things to look at, one more complex or novel than the other and didn't given them any instructions; just said, "Look." Actually, the results were fascinating. I never got to publish them. At that time, the major issue was paranoid versus non paranoid schizophrenia. I had this theory that the problem with paranoid schizophrenics is they were too interested in novelty, things that were different, and got stuck on that. It turned out to be just the opposite. The paranoids behave just like normals and the non-paranoids, however, significantly avoided all complexity, all novelty. They just couldn't tolerate it, which is an interesting finding. But I left it there.

The thesis got me a summa for graduation from Harvard. My parents came for graduation [1968]. The Shah of Iran [Mohammed Reza Pahlavi] was the commencement speaker. It was the first graduation in years that was rained out. So my parents had to be in my dorm room watching it from short circuit TV.

That really takes me then to Philadelphia.

KD: Wait, wait. Before we get to that, I'd like to circle back a little bit and even before you get to Harvard. Growing up, were there role models in medicine or academics? Tell us a little bit about your parents and your family. How did they spend their time and what were their values?

MM: My father was the sixth child, probably an afterthought of his parents, in the Asian side of Istanbul, observant Jewish family in a Jewish community. My grandfather, by the time I knew him, was really not all that lucid mentally. But it is said—well, it's a fact—that he had an antique shop and that he traveled to London to sell his wares on a horse and carriage. Actually, my mother went to Robert Academy, which was very unusual at that time for a woman. She actually had advanced placement so she finished high school in one less year than usual. She knew English, of course. She had gone to the English school, but at home, we spoke French, which was kind of like in Russia. It was the culture language at that time in the Middle East. Of course, in the street, Turkish, and at home when my parents didn't want me to understand things, they would speak Armenian or Greek and, then, of course, Ladino, which is Spanish, Jewish Spanish. So there were lots of languages, very cosmopolitan. There were no MDs [medical doctors] or scientists in the whole family at all, not even in remote generations. I really didn't intend to go into medicine at all. By the time I left Turkey, I was going into physics or some real hard science.

At Harvard, clearly, there were luminaries. I never really quite ever ran after luminaries. There were people who were instrumental because they were unbelievable lecturers. Rogers Albritton, for example, who lectured on Aristotle, was absolutely remarkable. Then, there was George Wald, Nobel Laureate.

[brief break in the interview]

MM: My degree was in social relations. That sounds like of funny but social relations, at that time, was a department at William James Hall in college where sociology, anthropology, and psychology were together. There were *big* names: George [correctly Roger W.?] Brown, the guy who invented flashbulb memory, George [A.] Miller, of course, ["The Magical Number] Seven Plus or Minus Two," working memory [capacity], and [Georg] von Békésy with Just-Noticeable Difference, [B.F.] Skinner's protégé, of course , Roger [correctly Richard J.?] Herrnstein.

It's interesting, I asked Hernnstein—I don't know how I addressed him—"Doctor Hernnstein, I want to enter psychiatry. What should I do? What should I prepare for?" He looked at me and said, "Oh, go and study some Sanskrit." It's only later that I realized what he was trying to say. Obviously, he didn't think very highly of psychiatry and what he was really saying is at that time, especially in Boston, very highly psychoanalytically oriented, that there was no scientific basis that would do justice to that and that anything you did was fine. Sanskrit would have been very good advice.

KD and LK: [chuckles]

MM: So things didn't move in any linear… I didn't have a role model to say, "That's what I want to do." That really came later.

KD: Were there people at Harvard University, Harvard College, who were invested in Freud in psychodynamic theory? The department, as you describe it…certainly Skinner was on the other end of the spectrum. Who was supporting that line of inquiry for you?

MM: You know, Kirk, I wish I could have said, "Such and such." In fact, there was *no* such person in William James, because ever since the days of [Karl] Lashley and William James, Harvard shunned the hard neuroscience approach to the brain. At that time, the only token person was Charlie [Charles G.] Gross who actually agreed to be my thesis advisor, because there was nobody else who knew much about the brain. There was just no one there. In fact, that's one reason that I chose that topic because, in a way, I didn't have to follow a party line. I had difficulty finding mentors. In fact, there was no one there who had ever measured eye movements in any such sort of thing or to combine it with schizophrenia. So it was interesting because my supervisors got excited about it. It was something that they hadn't gotten involved in.

KD: Was it unusual for an undergraduate thesis to involve the clinical population at that time? You had to have connected with people, is it, at the Boston Psychopathic Hospital?

MM: The Boston State Hospital.

KD: Was that a Harvard teaching hospital?

MM: Yes.

You know who was involved there? Simeon Locke.

KD: Really?

ML: He was seeing some patients there. It was one of these *incredible* state hospitals, huge buildings that you could get lost in and closed, locked, wards, of course.

What I remember is funny. Next to it, there was one of the most famous Jewish delis. So whenever we had time, we would go there to have a brisket sandwich that was really to die for.

Bernard Tursky was the person who made all of this possible for me because he ran the polygraph at Boston State. He gave me his research assistant to help me. It was really complicated in those days. I had to have two slide projectors that had to be synchronized to change the slides at the same time and have a marker on the polygraph record while the eyes were calibrated to go up and down. Since we used silver chloride electrodes, every time the patient had any sweating, there would be a drift of the baseline. So there were a lot of technical issues there. Bernard Tursky was the man who was *always* available. I don't think he had an academic degree. He was one of these engineers who got hooked into helping this. It's interesting because when I started medical school, I actually was asked to come back and teach the course.

KD and LK: [chuckles]

KD: I would think that up until that point, you didn't have a lot of interactions with patient populations, especially ones that were very, very ill psychiatrically. This was 1970, 1971?

MM: No, no. Nineteen sixty-seven, 1968.

KD: So even before that. What was it like being exposed for the first time to people who were so ill [unclear] Harvard College?

MM: The background for all of this is one of the most remarkable books that I ever read. I took a course by a man called Norman [F.] Watt who taught a schizophrenia course. One of the books there was called *Etiology of Schizophrenia* [Don Jackson, editor]. I highly recommend it. It was a compendium of all the theories then about schizophrenia. If you want the history of science… Obviously, there was the double blind theory, entirely psychoanalytical. Then, there was this unbelievable experiment of the Spider Zilla-x-Notata. What they did is they took two schizophrenics and non-schizophrenics and took serum from both. They had two groups of dead flies. So they injected the belly of the dead fly with either the schizophrenic or normal serum and, then, put them on spider webs and, then, showed that the spiders that came and sucked the abdomen of the schizophrenic serum-injected fly made irregular webs; whereas, the other didn't. This was really a genius experiment. Again, this was this mind/body dilemma. Is there anything in the body of schizophrenia that can explain this? That book really taught me about the relativity of scientific research, that you could be perfectly elegant and reach a completely different conclusion based on the method that you use.

It's after that course that I went to Boston State. I had already read about what you could expect in schizophrenia and, in fact, I couldn't even find half of that in Boston State because people were so medicated. My patient approach, I was very superficial. I don't even know who I asked. I'd say, "Is your patient paranoid or not?" That was the extent of my classification. It wasn't as if I had any patient interaction, as such.

KD: Neuropsychology was part of the Social Relations Department?

MM: Yes. All of this was in Social Relations. That Norman Watt's course was particularly fascinating because of the book. The book is a masterpiece.

KD: When you left Turkey at age whatever, seventeen, eighteen, did you think it was a visit to the United States and you would be back? Did you have any thought about what your trajectory would look like?

MM: Oh, yes, I think that was an ongoing refrain for years. I was *always* planning to come back. The first phase was after college and it didn't work out because I went to medical school. [pause] I had a girlfriend who wanted to make a decision, so I applied. Then, after medical school, also there were other things that came in, but always with the assumption someday I'll come back. Then, when I was at the BI, in fact, I had to go back because my deferral from the Turkish army had come to an end. If I didn't do that, then I couldn't maintain my citizenship, which I wanted to maintain. So I actually went back. There's a certificate there that you can see, the one at the bottom. I took my neurology boards in Turkey, which I passed, wrote the thesis, and went to the army, did my army stint in the tank corps and so on. That just shows you that I always had a real intention to come back. Just year after year, it didn't happen, even though I…

KD: You still have time, though, right, to go back.

MM: Yes. Yes. That plan is still on the front burner.

LK: [chuckles]

MM: I have people come in and train here. I go often to participate in conferences in Turkey, but spending time has not yet happened.

KD: Do you have family that are still in Turkey?

MM: Yes. I have a sister and two nephews. That's the only remaining family, but lots of good friends.

KD: Medical school… When did you decide you were going to pursue that? You decided you weren't going to be a physicist, but there were other options, I assume. Was getting a Ph.D. in the biological or other sciences in the list of possibilities? Why medicine or why medical school?

MM: Once that psychophysiology in eye movement issue came in, it was clear that I was heading towards biological psychology or in medicine. So I applied to MIT and Harvard, MIT psychology and Harvard Medical School. I got into both, but the first acceptance came from Harvard. I don't think I applied to any other medical school, by the way. In those days, things were simple. The Harvard acceptance came first. Again, there was the issue of making a decision. I didn't want to wait. I got into Harvard Medical School and the first two years, I must say, were really boring, very, very boring.

KD: So you didn't decide to go to Harvard Medical School by consulting the *Britannica* again?

MM: No. No.

LK: [chuckles]

MM: At that time, it was the simplest thing, because from Harvard to go to Harvard you don't have to… And there was another big advantage: in Medical School: I was a pre-med tutor in Eliot House.

KD: Ah!

MM: So I had a wonderful parking place right next to Eliot House. I had my Triumph Spitfire that I could drive to Medical School. I had more parking tickets in those years, but they were cheap in those days, so it wasn't that bad. Being a pre-med tutor was great. As an undergraduate, I was in Eliot House, so I knew people there and that made it less boring. The other side was that I didn't spend *any* time in the Medical School. I actually made almost no friends in Medical School because I was always back in Cambridge the first two years.

KD: It was boring because the curriculum was so elementary or…?

MM: Uhhh… [sigh] In college, I was on my own. I did things that I wanted to do. Suddenly, in medical school, there was a curriculum.

KD and LK: [chuckles]

MM: There were things that I had to figure out. You know, kidney physiology was fine. In fact, my experiment in the first two years was to figure out how potassium levels change, [unclear] level secretion in the kidney. It was interesting but there was no exploration. It was a prescription of what you needed to know. That's what didn't appeal to me very much the first three years.

KD: Was there a designated department of neuroscience yet? Or was it part of biology or was the brain not a part of curriculum?

MM: Gosh, it's so hard to remember. The people there in neurology, there were some heavy hitters. Obviously, [unclear] there and [Edwin] Furshpan and David Potter, Ed [Edward] Kravitz, Sandy [Sanford L.] Palay.

KD: Did they interact with the students?

MM: They did give lectures.

I believe it was during one of those years that I actually went to Norm [Norman] Geschwind's—the first time I heard him—lecture. I mention that in the piece I wrote for the BCH volume. It was during a snowstorm and, again, I had a great struggle with my Triumph Spitfire to go through the snow. I just left it in the street. I really didn't expect even classes to be on when I went to the lecture hall…very few people. Geschwind comes in with galoshes on, gets up, and it's another lecture. He really gives this classic lecture on pure alexia without agraphia. I was struck for the first time…the mind/body issue went beyond autonomic responses and come to the real control center. Then, of course, I was struck by his strange accent.

KD and LK: [chuckles]

MM: He had kind of a New York accent that I hadn't been exposed to. So that stuck in my mind. I think that was pretty much the turning point of where I went out of the psychiatry mode and, clearly, in the brain structure mode.

KD: At the time psychiatry did not include the brain? At that time, was it mostly, at Harvard, psychodynamic or was it psychopharmacologic or neither?

MM: There were several. The MMHC [Massachusetts Mental Health Center] was to psychoanalytical but, at the same time, really some basic dream anatomy with [John] Allan Hobson and [Robert] McCarley.

Then, at McClean [Hospital, Belmont Massachusetts], there was a very interesting movement. Of course, the big name there was Seymour [S.] Kety. Actually, Seymour Kety is one of Lou [Louis] Sokoloff's colleagues, so the two of them made what we now call FDG [fluorodeoxyglucose] PET [positron emission tomography] possible in a quantitative way. Then, they were both colleagues of Julie [Julius] Axelrod who got the Nobel Prize, one of whose students is [Richard J.] Dick Wurtman, who together with Norm Geschwind was very instrumental in my choice of career. The other big name at McClean was Bob [sounds like Viss-er-ee-nee], who was, of course, a transmitter person.

So there was the psychoanalytical approach, dream, but none of them really took the brain, supratentorial brain, serious. The brain stem with transmitter pathways…but to really ask the question if is A connected to B to do this and that, there was none of it. Actually, Geschwind was the person who brought that in. Even in [David H.] Hubel [Torsten] Wiesel [*Brain and Visual Perception: the Story of 25-Year Collaboration]* what were we talking about? We were talking about simple, complex, hypercomplex cells that

barely are able to tell you if something is a straight edge or not. It was a different stage altogether.

KD: Did your rotations in medical school and neurology and psychiatry have an impact or did you know where you were headed even before you started your…?

MM: Oh, I think that was a big impact. For the psychiatry rotation, yes, I was at MMHC. I forget his name. There was a very good psychoanalyst there and, of course, the other person that was there was [Daniel H.] Dan Funkelstein. He interviewed me, by the way, for medical school.

KD: A stress interview or regular?

MM: It seemed to me it was very comfortable.

I don't remember but the neurology, I definitely remember. The neurology, again, was one of these things that is kind of apocryphal. I started my rotation at BCH. The first patient I was sent to examine had pure alexia without agraphia, and I found out the patient was also amnestic. At least in those days, life was beautiful because you didn't have an fMRI [functional magnetic resonance imaging] scan, so you could say anything you wanted to. There was no one to dispute. So you would say, "Here's a patient… pure alexia." Guess what? Left occipital splenial, and, of course, the lesion went into the hippocampus. [unclear] cerebral. We didn't know.

KD: There were no pneumo encephalograms?

MM: How can you tell with pneumo that kind of detail?

KD and LK: [chuckles]

MM: It was just enchantment, because you would listen to [Derek E.] Denny-Brown or Geschwind or whoever gives this erudite description of what the mechanism was and that was the end of the story. No challenge was possible. It made sense. It was fun.

KD: [unclear] it's still fun even though we can challenge.

When you were applying to residency was BCH the obvious choice and, if so, why?

MM: I remember that again. I was in rounds at HUP [Hospital of the University of Pennsylvania] in Philadelphia. At that time, there were PA [public address] systems, so the PA system said there was a phone call for me. I left rounds and I took the phone call. It was Geschwind calling saying, "Would you like to be a resident in neurology?" I said, "Yes." And, as far as I know, that was the entire application. Plus, I didn't apply to anything else. I didn't even know what I thought was going to happen if this didn't work out.

KD: How did Geschwind know that you were interested?

MM: Well, I spent a lot of time with Geschwind [unclear] the last two years in medical school. Actually, I had already done a number of research projects and we may get to that. So by that time, we had a very close relationship. There was no formal application process, nor did I consider any alternative.

KD: You were one year in Philly. Then you came back to Boston.

MM: Yes.

KD: How many people were in their residency program at that time, entering class?

MM: Interesting. There was [Stephen] Steve Waxman. There was [Andrew G.] Andy Herzog, [Michael P.] Mike Biber, Elliot [D.] Ross. [pause] And a person I can't remember. He became a hand surgeon [If remembered, perhaps, the given and surname could be entered here]. Rémi W. Bouchard was there when I was a student. He was one of the chief residents. Maybe Biber was when I was a student rather than when I came back. David…no, some Oppenheimer [Edgar Y. Oppenheimer], a pediatric neurologist. [Albert M.] Al Galaburda was one of the residents. Then, Jesus… I forget his last name. [Jesus Velez-Borras] He became a neurologist in Puerto Rico. Oppenheimer was the pediatric; there was one pediatric person. Then a couple people whose names I just don't remember.

KD: The senior staff was Geschwind… Denny-Brown was there?

MM: Of course, as you know, there were Saturday rounds, so Denny-Brown would come for some Saturday rounds to get some patients. Patients would be presented to him. He would discuss. Geschwind led, but the real clinical go-to person was [Thomas D.] Tom Sabin and, then, Simeon Locke would come to do Tuesday professor rounds. Paul [Ivan] Yakovlev was on the top floor with [Thomas L.] Tom Kemper, so he could still be consulted on occasion. [Jerome] Jerry Lettvin used to come to do some professor rounds. Leon Eisenberg, a person who with Leo Kanner really sort of put autism on the map would come on occasion to do rounds. [sounds like Sigh-met Luh-sell] would come to do rounds. The permanent staff was really small but the visiting staff was very interesting. Oh, Ira Sherwin was the electrician, the EEG [electroencephalography] person.

KD: Maybe you could talk a little bit about the transition. It sounds like you were already tightly involved with the group before you left. Tell us a little about that and, then, when you came back, you had a new set of responsibilities. You were not a med student. You were a resident who had different time demands. Tell us about that period.

MM: Very interesting… I think that really was the most formative period of all. I had listened to this lecture by Geschwind, so, clearly, I was interested in that approach. Then, when I saw my patients on the wards, it got me really to believe that these things existed.

KD: Did they set you up?

MM: No. I think it was one of these providential things that happened *or* that's the way I remember it. Who knows?

Then, the second thing was I decided to take an elective by Dick Wurtman that was given at MIT. That's how I got to know, also, [sounds like Ann Gabriel] and Walle [J.H.] Nauta. Dick Wurtman had a course that was, essentially, neurotransmitter related, how you synthesize serotonin, norepinepherine, *acetyl*choline. But while he was doing that, there were chapters there about how do you make the hippocampus influence hormonal and transmitter metabolism through the relationship with the limbic system. At that time, it wasn't limbic; it was hypothalamus.

Then, somehow, I heard the H.M. [Henry Molaison] story with the hippocampus and memory. So, suddenly, I got interested in the hippocampus and I wrote my paper for Dick Wurtman on the anatomy of the hippocampus. I got to read these absolute classics of [Rafael] Lorente de Nó and [Franz Joseph] Gall on how they got the anatomy. Here was then the hippocampus and the amygdala in the Wurtman course doing these things to transmitters and endocrine.

The Geschwind idea of connectivity, the H.M. story about the hippocampus, and, suddenly, I had this question. I said, "To do all these lovely things again, the mind/body issue, how does the hippocampus know about what's going on in the rest of the world without a connection between the hippocampus and the rest of the cortex? So I went to Geschwind and I said, "Tell me." He said, "I don't know, but there's a guy upstairs on the tenth floor, [Deepak N.] Dee Pandya who just came in. Maybe you can go and ask him."

So I went up there. He was in the dark room developing some photographs. In those days, we developed all our photographs. He came out and he said, You know, it's an interesting question. I have a hunch." Of course, down the [unclear] was Gary [W.] van Hoesen who was studying the relationship of entorhinal cortex to the hippocampus. He said, "I have a hunch that the presubiculum is the link between the cortex and the entorhinal cortex. So it would be the cerebral cortex, presubiculum, entorhinal cortex, hippocampus. But there's no proof. Let's do that. Would you like to come to [unclear]? I have five squirrel monkeys. We'll do [unclear]." In those days, the only thing you could do is lesion [unclear] degeneration of the Nauta method. I said, "Fine." So we'd go there. They had five squirrel monkeys. We anesthetized them. There's the stereotaxic frame. We go in with the coordinates of the presubiculum. We make a little lesion. I was in hurry because I was going to go to [sounds like Brown-stahn]. I was starting to get in love with [sounds like Brown-stahn] through my roommate. We finished doing all that. He was an incredibly generous mentor. He really handled me like a colleague. Actually, he did the work of a research assistant for me as I was doing those things. Then, we had to wait for this two weeks. You wait for two weeks. You sacrifice the animal. The brain has to go be perfused in formalin for several weeks. Then, you

have to cut it into twenty micro sections, then stain it through a very, very elaborate silver impregnation method. So all of this and the day of reckoning came and we had missed the presubiculum in all five monkeys. It wasn't good news. But, then, I found out that, while we missed, all five animals made a lesion in the medial geniculate nucleus of the thalamus.

So we said, "Well! Let's write a paper on the medial geniculate"—which is the nucleus that projects to the auditory cortex—which I did. It was published. ["The Projections of the Medial Geniculate Complex within the Sylvian Fissure of the Rhesus Monkey, 1973."] I actually presented it in the Boston Society for Psychiatry and Neurology the first time. I still remember being very anxious about it. It was a stormy evening, very, very few people braved it. As I was starting, Denny-Brown walks in, so, obviously, this makes the whole exercise more meaningful. I gave my paper and, then, Denny-Brown really liked it. That made a difference. That paper still is quoted. It was published—I don't know—in 1972. It's still quoted as a legitimate finding.

That's my interaction and, at that time, I was really telling Geschwind what was going on. I got to work with Dee, and then with Gary a lot.

KD: Did you try to find the presubiculum another time?

MM: Not really. Well, it's interesting because we had lots and lots of material. As I went through, I sort of patched together the way things were going, that it was cingulate presubiculum. [unclear] cingulate [unclear] cortex, presubiculum entorhinal. Actually, I wrote the outline of a paper how to do that and just the week after that in *Brain Research*, a guy called [Michael T.] Shipley published the same thing. So we just stopped at that point.

KD: So you return to your family as a resident far more [unclear], presumably, than you were as a medical student doing [unclear] time. So how did you manage to sustain your [unclear] research? Do you take care of patients or was there plenty of time for both?

MM: [sigh] I was, of course, privileged because I came in and they immediately gave me a desk on the tenth floor. My desk actually was a wooden table which Denny-Brown used as his operating table. Denny-Brown was famous for his thrift.

KD and LK: [chuckles]

MM: He didn't believe in any expensive thing. In fact, this is Denny-Brown's operating light.

KD: Nice.

LK: Wow.

MM: So there was my light. There was my desk and I had Stanley Cobb's microscope. Everyone was there to help. It's really like they were my assistants and we did research. That's how I developed the silver impregnation method in the human brain through our first studies of patients with spinal lesions and anterior choroidal inference and so on. In fact, I developed the HRB [Halstead-Reitan Neuropsychological Battery].

KD: As a resident?

MM: Yes, of course, because… [pause] Yes, I think so, because the AChE [acetylcholinesterase] and HRP [horseradish peroxidase] paper was published in 1976 and the move to the BI, I believe was in 1976.

KD: So with that work were you explicitly looking to be able to start and go backwards? How did you figure this out?

MM: Which? The HRP?

KD: Yes.

MM: You know I spent a lot of time with the Nauta method. So, by that time, I was pretty knowledgeable about its limitations.

KD: Just briefly explain the Nauta method.

MM: You destroy cortical area and, then, the axons of the neurons that die degenerate. This is Wallerian degeneration. You can use a very elaborate way of impregnating only the degenerated axons with silver, which you then develop just like a photographic plate and you can see the degeneration in terms of little broken silver impregnated axons. This allows you to trace the connection of the area that's [unclear]. The problem with that, of course, is that it's now very sensitive and, secondly, there's the big issue of so-called fibers of passage. If you destroy an area like this, there's a [unclear] bundle that's growing there, you're going to see degeneration there as well as there but the two are not necessarily the axons of the area that you destroyed.

Around that time, there were major new discoveries. One was [William Maxwell] "Max" Cowan and his people who came up with the autoradiography method where you could inject tertiated amino acids anywhere. Only the cell bodies would take up the tertiated amino acid and, then, the ribosomes would turn that into protein, which would be transported [unclear] in the smooth *endoplasmic* reticulum at the rate of about 400 millimeters a day. So you would wait for about a week and, then, sacrifice the animal, cut the sections, and develop it like a photographic plate. The terminals where the protein had been transported would emit beta radiation, which would then reduce the silver nitrate and you would see the silver precipitates and you could get the idea. The fiber of passage was no longer the issue because only cell bodies develop.

At the same time, [Jennifer H.] Jenny Lavail, who was at Children's Hospital across the street, developed the HRP method where things went the other way around. You injected HRP at the endings, will be [unclear] psychosed, and, then, transported retrograde into membrane called the vesicles to the cell body. So you inject it anywhere you wanted to. It would, presumably, only be taken by endings and you would see the cell that projects. So, suddenly, we had *unbelievable* new tools to look at projections.

So my role there was to look a little deeply into the HRP method and to figure out that, based on my prior knowledge with the anterograde methods, Jenny Lavail's method visualized a fraction of the connections we needed to see. So I spent a few years both at the BCH, and then at the BI I believe, to improve both the histochemical sensitivity and, also, the uptake of HRP. So there were several manipulations, including using a different chromogen called tetramethylbenzidine, which I discovered in the cancer literature. It was used for detecting occult blood in feces. We developed that into something usable for HRP and, also, I conjugated the HRP to wheat germ and gluten to make it easier to be uptaken and transported. Suddenly, it was a new world. This paper ["Ultrastructural evidence in mice that transganglionically transported horseradish peroxidase-wheat germ agglutinin conjugate reaches the intraspinal terminations of sensory neurons," 1982] has now been cited over 4,000 times. It's a citation classic. People started to study the projections of the gut, the heart, the trachea, just name it. The whole body became open to this kind of…and there was no other method that could make that possible.

So between these two then started my neuroanatomy career, because now I had the tools and I could address some pretty hairy anatomical questions which, at that time, was the projection of paralimbic areas, which was the big bridge between neocortex and hippocampus and amygdala. So I gave the insular to Elliott [J.] Mufson. We had a series of papers we published which still is, I think, the major paper on insular projections in the monkey. Then, [sounds like Ah-soon More-on], who was a post doc from Spain, was given the temporopol project and, then, [Robert J.] Bob Morecraft [unclear] project. These really just completed. Then, with Dee, I was working on the cingulate. So we had the whole paralimbic, the [unclear] cingulated, parahippocampal-temporopol, [unclear] covered. That was my neuroanatomy laboratory at the same time that we were developing cholinergic pathway anatomy.

KD: So I think we're now beyond your residency, at least some of it. But to step back, thinking about how people try and use this. For a long time, they were doing thirty-six, forty hour days. The turnover of patients is really rapid. To be in a hospital, you have to be sick unto death. If your residency program had those kinds of demands, do you think you could have spent as much time in the lab? What was it like being a resident in terms of your clinic responsibilities?

MM: I don't know, Kirk. I think that although it was not all that great… I was up at night.

Oh, by the way, I didn't stay in the hospital because I rented a flat right across from Boston City, so I would go home.

KD: They had a paging system, not overhead then?

MM: They had a paging system by that time. I had a pager.

I think all the merit and all the credit goes to Geschwind, van Hoesen, Pandya, who really just allowed me…leveraged my little time by really accepting me as even more than a colleague. Now that I think back, I sort of really kind of told them what to do. [chuckles] And they would just do things. So I would go there and there was material ready. I would look at it. Time was leveraged. I didn't do any heroic extra time, other than the usual thing. I stayed up thirty-six… Boston City in those days was very primitive. In the middle of the night, if a patient had some stroke-like thing, I had to push the bed to the radiology suite down the hallways. There was the carotid stick and so on and so forth. We were busy in our own way. Somehow, there was time.

KD: The other people in your training, who are a very impressive group, were they also supported in the way or in analogous ways? Was that the environment or were you just in the right…?

MM: Andy Herzog became the closest, so he did some productive things with Gary on the almygdala. It's not that I was privileged. It's that my interests somehow really synchronized with Gary and Dee, so it was in their interest and they used my clinical knowledge to sort of put their findings in context. I had done a fair amount of reading at that time and I had some knowledge on patients, so it helped them as well to have that context. Think of it. It was like the Wild West, because no connections were known so anything you found was knew. Discoveries were just all over the place. It was like the very early days of functional imaging. The only difference is that functional imaging is irreproducible; whereas, anatomy is there forever. Once you [unclear] finding, it's eternal. Those were very heady days.

KD: Absolutely.

Tell us a little about your relationship with Denny-Brown and tell us a little about Denny-Brown. You knew him toward the end of his career?

MM: I can't even say I knew him. I attended conferences. Of course, Portia [sounds like Tall], who was Geschwind's secretary, was Denny-Brown's secretary. We had some stories of Denny-Brown. He came to my lecture on the medial geniculate, so I had a few words with him at that time. But, by that time, he was sort of one of these untouchables. It was not clear where his head was all the time. He was too respected to kind of be in a conversation that was meaningful. Geschwind always had tremendous respect for Denny-Brown. Geschwind didn't suffer fools and had choice words for a lot of people, but for Denny-Brown, he had nothing but respect.

KD: Talk a little bit then about Norm Geschwind. What was his relationship with you, your colleagues or the trainees? What role did he play in your career?

MM: He was a lecturer, very important, which made me then read the Disconnection papers [Disconnexion syndromes in animals and man," 1965]. That was it. I think the Disconnection papers is what… I still think in those terms. So I would say that's about as important. He was always supportive.

When we moved to BI, the move was not one hundred percent pleasant. There were some hard feelings, having to leave Tom Sabin behind. The only people Geschwind actually took with him were Andy and myself.

KD: The move was because Harvard was leaving Boston City?

MM: Harvard was kicked out of BCH because, at that time, there were three of everything: Tufts, BU, Harvard. Harvard had other hospitals. The City decided Harvard doesn't need yet another one, so moved out. The only people… No, no, Steve Waxman. Oh, [Benjamin P.] Ben Seltzer. Yes, a very important name.

KD: Yes. He was one of the trainees.

MM: Yes, he was definitely…yes, one of the residents. Sure. Ben also got a lot of mileage out of the anatomy people.

The move was Geschwind—I was still a resident, third year resident—Herzog, Ben, Steve Waxman, Gary, and Dee. That was it. So the people left behind were Tom, Galaburda, and a couple of other residents, the other faculty, so it was very small. We came in to [Louis R.] Lou Caplan, who was headed of neurology at BI at that time, and Chaim [I.] Mayman.

At that time, a coincidence, a bad coincidence: the first year we moved. Geschwind was not a good negotiator. He was sort of politically not all that savvy. We had very little space, very little anything. And, on top of all of that, the first year we were there, he went on sabbatical to Queen's Square. Here we were a new department, no protection. Then, he sends a letter—I don't know where I have it; I once had it—a big letter handwritten to Portia [sounds like Tall] to tell me to start the BNU [Behavioral Neurology Unit] which is how it started. I, basically, had this letter, so I go to…

KD: You're a third year resident? [unclear]? You were early on?

MM: Either a third year resident or it's my so-called fellowship, which was certainly never official.

KD: [chuckles]

MM: I think it was maybe that fellowship year.

LK: Around 1977, maybe?

MM: Yes. Yes. I went to the hospital. They gave us three rooms that was right next to chest therapy at BNU. So every time we examined a patient, they would do this chest massage and people expectorating. It was interesting.

Then, Geschwind came back. He really didn't get involved in BNU activities that much. At that time, his reputation was really coming on all over the world. [pause] Then, Geschwind became obsessed with this testosterone issue. I never understood what really got him into that. It was an obsession.

KD: This is his view of testosterones role in the developing brain?

MM: Yes. I remember I would go there on Saturdays to my room to escape, so that I could have some time to get a few things done. I would hear steps. Geschwind would be going towards his office. It was just here and mine was there. A knock at the door. He'd say, "Oh." He'd open the door…a two-hour discussion about the bursa of the Fabricius and why one testicle is more descended than the other. He was just completely into that and really almost removed from bread and behavioral neurology.

KD: I was thinking Geschwind got obsessed by ideas all along, including when he was saying about connections and disconnections. Was that his style or was this somehow a surprise?

MM: I don't know. He really had the ability to put different things together to create an interpretation which others had missed. So, this was, I suppose, part of that but it was at a different level than the others. The other thing about Geschwind is that reading the Disconnection Syndrome, you would think this man is [unclear] anatomy.

KD: Right.

MM: He never went up to the labs. They were one story up. One day, I had just developed my HRP method and I had this *beautiful* preparation. I'd injected the olfactory bulb, so we had the periform cortex in the anterior olfactory nucleus. *All* the cells were retrograde labeled. You could see the dendrites. Then, there was also anterograde projection so that the entire band of terminals was… At that time, I was using a blue reaction product for HRP. [unclear] counterstain the sections red. So there was this red/blue. It was just gorgeous.

KD: [chuckles]

MM: So I asked him to come to the microscope. This was at BI. He's at the microscope and I don't see… I expected his face to just light up. I then realized I think he was colorblind.

LK: Ohhh.

MM: I had to confirm that with one of Geschwind's nephews. I think he kind of said that or then I figure it out. He didn't like to look through the microscope. He just didn't do it even though Gary and Dee were just coming up with proof of his Disconnection papers. You would think he would be there waiting for the latest installment.

KD: Yes.

MM: He was interested more in the *idea* of the connections than in the real nitty gritty.

LK: You said that Geschwind wasn't very political. Then, when he returned from sabbatical, he was very consumed with his testosterone research. I was wondering if you took on a de facto leadership role in starting the BNU or who really was really fighting for that.

MM: The BNU, yes. The BNU, I started and I continued, but in the department, no. In fact, when he died and I got to be acting head of the department, I must say that really I had other things to do. That was just not something that I could do well or with any degree of success.

KD: We'd like to talk about the birth of the BNU, but before, since we are talking about these major figures in neurology, what would you say Geschwind's most important contribution is to the field that we love, behavioral neurology?

MM: The Disconnection papers. It is just a masterpiece. It's the single most important publication in the field of behavioral neurology, which didn't exist before, and, then, the pieces that led to it. So his callosal disconnection paper ["A human cerebral disconnection syndrome"] with Edith Kaplan, his asymmetry paper of the planun temporale ["Human brain: left-right asymmetries in temporal speech region," 1968]. Then, his paper on *pure alexia. That's where [unclear] color anomia, I believe with* [Michael] Fusillo. His paper on the shrinking retrograde amnesia with [D.] Frank Benson. You can think of the Disconnection papers here and these are all the satellites that come through it. It's a corpus that anybody in behavioral neurology that hasn't read that paper is doing it at their own peril. That's the fundament of what we're about. Now, he did *not* talk about networks. That was later. He always considered a simple hierarchy, A to B to C, never dealt with the feedback top down projections. He didn't deal with the dynamic aspects of neuro connectivity, but those were at his time not ideas that were there. Then, Geschwind was an *unbelievable* logocentric person.

KD: [chuckles]

MM: For him, everything was *the word*. He didn't realize the right hemisphere specialization for attention, for example. He thought it was a disconnection syndrome, because the right hemisphere couldn't communicate to the language hemisphere. He missed the entire [unclear] agnosias, you know, [António Rosa] Damásio's prosopagnosia story. He just still thought that that was a disconnection from the verbal areas rather than a separate object processing system. So there were lackings, sure. On

the other hand, for its time and the way the corpus built up to an entity, it's unparalleled. That's it. That's basically the single most important and I had the opportunity to work with him at the time when these ideas were all very fresh. He was a very generous person who definitely left me enough time. It was like being back in college. I had very, very few duties.

KD: Were you, at that point, being supported by grants or was the hospital…or Geschwind had some sort of ways to support faculty?

MM: I don't know. You must understand that my salary then was $6,000.

KD: That sounds like a lot.

LK: [chuckles]

MM: I never asked.

KD: Where it came from

MM: The city has slots. We were a city hospital. When we moved to the BI, I did get an NIH [National Institutes of Health] fellowship to study the projections of the septal nucleus after I finished my residency, so there was one year of support there. Oh! then I got a grant from the Free Masons. What was his name, the guy who was a psychiatrist at McClean? He was running this. What was the name of the outfit? [If remembered, name could be entered here] So I got a very hefty grant at that time: $20,000 a year for three years. So that supported me for quite a while, including a research assistant and so on. Then, I got my first grant. I'm happy to say I've been continuously funded with no interruptions since then. It was good.

KD: Very good.

Boston was a multi-hospital town. Not only was there the three medical schools, but we had Harvard unlike most places. There were multiple department heads. What was the relationship like between the hospitals? Geschwind was different than I think the other chairs. Did it matter? First of all, how did the MGH [Massachusetts General Hospital]…? I believe [Raymond D.] Ray Adams probably was the chair at the time. What were their interests? What was their focus?

MM: Well, of course, as a student Ray Adams played a major role in the teaching of neurology. But in the inimitable Ray Adams' way, he never came to lecture to the medical school. We went to the MGH to hear him lecture at the Ether Dome. So he definitely played a role.

Again, another memory that sticks with me in days again before CT [computed tomography] scans and so on… [Edward Peirson]. E.P. Richardson [Jr.] and Ray Adams, a brain uncut. The usual hierarchy: the resident presents; a medical school student says

something not very bright; then the first-year resident; then second-; then third-; then junior faculty; then senior faculty; and then Adams makes his [unclear]. I think he says, "This is a hypothalamic hamartoma." A hypothalamic hamartoma? They don't grow on trees. It's a closed brain. There's no imaging. So, we say, "Oh, sure," you know.

KD: [chuckles]

MM: E.P. gets up in his usual kind of quiet but authoritative way, takes this brain and he cuts and cuts. Suddenly, as he goes to the base of the brain, we hear the knife going against calcified something. It's really one of these…you just say, "It's not possible." He opens it up and there's a harmartoma.

This was the kind of person that Ray Adams was, but the one difference from Geschwind, who was frequently wrong in his diagnoses, was that Ray could *never* explain the mechanism of his diagnoses. He couldn't tell you, "This is what this person has and the mechanism is that the cortex doesn't connect to the thalamus which doesn't do that." Geschwind came up with diagnoses that were not always correct. But even in his incorrect diagnoses, the mechanism he gave was so elegant that it didn't matter.

KD: Do you think it was a difference in mission or Adams was more conservative?

MM: No, no. Adams was not interested necessarily in the mechanism. He was a real doc, so he had a diagnosis to make. He was incredible in his ability to make a diagnosis. He probably didn't feel it was worth his time to speculate on mechanisms since you could never really prove what he was postulating. Whereas, Geschwind was always interested, as was Denny-Brown. [unclear] in coming up with using a patient. Every patient is an experiment to kind of explore brain behavior relationships.

KD: With Adams and [Maurice] Victor [unclear] using encephalopathy. They argued over where the lesions were. Did they not then take it to what these areas were participating in? It was just an observation.

MM: You know, it's interesting. You read that book [Principles of *Neurology]*, which is another classic, the question comes up. Is it [unclear] or is it medial [unclear], medial dorsalis? But, then, beyond that, why? It's even that controversy: the whole issue of the eighth circuit and so on and so forth. Now, I read that book many years ago. But if I remember, there was not the strength of that [unclear]. So that's where the distinction came in. I had *very* little interaction with Victor. I don't know if he was there by the time I was there. But Adams and, especially, E.P. Richardson were major, and, of course, C. Miller Fisher.

KD: Right.

MM: These were all part of my medical school, too.

KD: People who trained with Fisher say that he would spend hours with a patient trying to sort out and describe what he observed and connect either known or hypothesized [unclear] to behavioral, or cognitive, or other changes. Did you have any [unclear] of him?

MM: Not personally. I don't know if you know that he was very closely related with Jay P. Mohr's studies on aphasia. Actually, he wrote the preface with Mohr on the volume on aphasia [perhaps, title could be entered here]. Of course, he wrote books on confusional states and so on. So he was definitely interested in behavior. I had very little interaction with him.

KD: Did the leaders of the various departments, to the best of your knowledge, play well together or was it pretty parallel?

MM: The structure at that time was there was an executive committee of the neurology departments and I was a member of that committee for years as acting head of the BI. Charlie Barlow was the head of the executive committee.

KD: Right.

MM: Then, there were the other chairs that got together once every month, I believe. They knew each other. I think they respected each other. But in terms of interactions, at least what I remember, it was miniscule. Well, of course, when we moved to the BI along with the training program, it brought us together. There were joint grand rounds and residency programs and so on. As years progressed, then what really brought the departments together were themes. For example, once Alzheimer's Disease became important, then the BI became part of the Alzheimer's Disease Center with John [H.] Growden at the MGH. We had a lot of interactions with Dennis Selkoe, with Bruce Yankner at the [Boston] Children's [Hospital], so, suddenly, things came together. But it wasn't structural. It was based on a common theme.

KD: Shall we talk [unclear]?

LK: We've been going for about an hour and half. I didn't know if anyone needed a break or if we're good to keep going.

MM: It's really up to you.

KD: Why don't we talk about the Behavioral Neurology Unit's birth and, then, take a break…

LK: Okay.

KD: …since that is sort of on the table or was.

You had described that Geschwind sent a letter to his secretary from Queen's Square or wherever he was that you should start the Behavioral Neurology Unit. Then, what, if any, models did you have? How did you decide what should be included? You didn't really have much space, clearly. What was the unit at the time?

MM: [pause] I knew we had to have a psychiatrist. Yes, I think the letter had some kind of sketch saying what some of the parameters would be. I don't remember, but, basically, what I had in mind was David Bear, at that time, was developing his ideas about temporal lobe epilepsy. So we definitely wanted to have that, so he was one. Then, we needed a neuropsychologist and Geschwind said, "I'm going to send you a candidate," and [Sandra] Sandy Weintraub walked through. Again, in those days, you know, we had no searches. We had no interviews. People just…

KD: Showed up.

MM: You'd just simply say, "Come." We didn't even talk salaries. There was no contract. Just people came. We had to have a secretary assistant to schedule patients. The first one we had was a remarkable woman. I think Laurie was her name. She was Orthodox Jew, so she had to leave early on Fridays. Her real skill was that she could drink beer while standing on her head…

KD and LK: [chuckles]

MM: …which is a rare skill to have.

KD: Most of us don't test whether we have that skill or not.

LK: [laughter]

MM: She really was part of the birth, because she was a rallying point.

Then, I had to have a social worker [unclear] was that early. Then, another neuropsychologist who came in was Betty North. Ben Seltzer, occasionally I think, was scheduled to see some patients, but he was not part of the team that moved to the BI. He was, I think at that time, at the V.A. [Boston Veteran's Administration]. That was it. We had three rooms and we would schedule patients and I would see patients. I don't know how they called to schedule. I really don't know how things started.

Then, the next big step after these three rooms where we saw patients is when I started the fellowship. That's where things started to then grow. My first fellow was John [sounds like Tell-ish], who was a remarkable young man. He used to send, for years, contributions to the BNU. He did not specialize in…and he was probably the only one that did not. Then, the fellowship increased, of course, tremendously increased the scope of the unit. Actually, the fellows were the life of the unit.

KD: Before we talk about what is very important, the fellows that you trained… You said that you had to have a psychiatrist and a neuropsychologist. Why? At the time, there were in-patient centers like at the V.A., the memory unit, I assume, where they would take strokes who were on the unit and they would attend to them. What was out patient behavior neurology? What did you think it was going to be?

MM: There were several movements there that were becoming clear. We couldn't have the V.A. model because in a private hospital, we still needed to justify admissions through needs and, then, people in the hospital didn't just rush to give us patients. We felt that we had to have our own catchment area to see and treat patients that were of interest to behavior neurology rather than rely on in patients—though we had a presence in the in-patient. [unclear], you know, attended. I think by that time at the BCH, we did not have neuropsychology, which is quite remarkable. None. Our psychiatry was very, very sporadic. If we referred, it would be general psychiatry, which would be very well used. So I really can't tell you how that…but it was clear by the time I started that I had to have a psychiatrist and a neuropsychologist. I had no doubt about it. The social worker came a little later when it became clear that we had psychosocial issues with every patient that had to be dealt with. That's when things started with very little prescription. It just happened. There were no other models for that. I don't think there was anything like it, because, again, things were departmentally ordained. The V.A. was a totally different system. There was a research [unclear].

Things were very haphazard in the beginning, very haphazard. There were days when we had nothing to do. There were days we saw patients [unclear] didn't know what to do. We had lots of discussions. The CT scan was just getting into…so we had that available, but the pictures were abysmal at that time. We had some SPECT [single-photon emission computerized tomography] scans. Again, very primitive. We didn't have really all that much, but we had a lot of energy. We knew that this was a new field. Dementia was a rarity. We still saw things… For example, I got very interested in kids who were shy. We saw a lot of temporal epilepsy. Tourette Syndrome was one of the areas. So we saw all kinds of different patients who didn't fit any of the other established subspecialties. And people from other disciplines started to send people to us…stroke, epilepsy, and so on.

KD: Did you view the mission as a place that would evaluate and then care for patients who had brain behavioral issues or did you view this as an opportunity to do clinical research or both?

MM: Again, there were things that you didn't question at that time. At that time, the triple threat was a way of life. I was teaching and I was a neurologist and I had to see patients. I had to treat patients. We were very treatment oriented. Epilepsy was treated. Tourette was treated. We were a medical system. We were writing prescriptions, getting blood levels, and [unclear] patient's [unclear]. It was a medical service just for a different kind of patient. The research really at that time, I didn't have much clinical research. My research was totally different. At that time, the lab was somewhere else.

So for quite a while, the relationships were sort of in one's mind but not in any direct way.

KD: In terms of the relation between neurology and psychiatry, what was happening in the late 1970s when you develop this? Was the department at the BI in psychiatry open to the brain at the time? David Bear came from the outside?

MM: Oh, yes, David Bear was an outsider. The BI, at that time, was led by [unclear] [unclear] was a psychoanalyst. That's what he was. There was very little interest. I think Geschwind must have had some discussions with [unclear] and [unclear] just not interested.

KD: Did David Bear not join that department?

MM: [pause] He was kind of peripatetic.

KD: [chuckles]

MM: He moved around. He was never full time at the BI by any means. I don't even know if he had an appointment. We didn't worry at that time about these things. I really had full freedom to bring in people without worrying about appointments, without worrying about the [unclear] boundaries. It was interesting. It was much, much less bureaucratic.

KD: You started the conversation talking about Freud and your interests. The BI was psychodynamically oriented. They were interested in the brain. Were you still interested in trying to understand the neuro systems underlying some psychoanalytic concepts or had you moved to other thoughts?

MM: I was never tempted to write the neurology of psychoanalysis, for example. There have been people who have written such, in fact, quoting me.

Alfred Russell talks about logical types. To over simplify what he says… It's not a good idea to use evidence that one level to then explain things at a different level. The best example is if I look at a Picasso and I feel this is great. Somebody says, "But, you know, let's take a spectrophotometer and look at different wave lengths at each square millimeter." You could do that. But then to use that information and say, "Why do I like this picture?" would make no sense whatsoever. So I think reduction is one direction. I don't think at this time we have any information that would do justice to the beauty of Freud's system. The question is it true or not true is immaterial. He had a model, but it's at a different level. I don't think that the kinds of information we have in function imaging or anywhere else speak that language. It's a different level.

KD: How did you bridge how you spent your time in your lab, which was doing basic, I think, more anatomic research with the patients that you were seeing right in front of you?

MM: For a long time, I just didn't think that that was necessary at all. This was here. I never did anything about the anatomy of Tourette.

The one linkage really happened in spatial attention, so that, too, happened at the BCH. Again, it's this one patient and I don't know if it was at the BCH or not. [pause] Maybe it was at the BI. There was this guy who had severe neglect for the left side. He had right hemisphere [unclear]. So they would bring him his tray and he just wouldn't eat food on the left side. So I asked the nurse to starve him for a day, not give him food, and, then, put the tray again. This time he ate what was on the left. I got interested in this motivational aspect to spatial attention, but there was no anatomy. At that time, my HRP system was developing and we could now, for the first time, look at cortical connections. With Jenny Lavail, we had looked mostly at sub cortical projections. So I injected the [unclear] in a money area PG [inferior parietal lobule]. We found—neglect is supposed to be a parietal syndrome—in addition to the other cortical connection, there was a connection from the limbic part, retrosplenial cortex and the cingulate. That was the limbic connection. That was tied to my interest in spatial attention. The paralimbic areas went into the [unclear] epilepsy story, but indirectly. It's only now where there's much more relationship between my interest in tPA [tissue plasminogen activator] and imaging, but that's because imaging has now substituted for anatomy. It's not so easy to do basic anatomy in a way that's directly relevant to cognitive neurology.

KD: Because?

MM: Again, the connectivities are immensely complicated. To try to figure out the anatomy of word comprehension, I think today is beyond any method that we have. I can't go in there and do an anatomical experiment. First, there is no anatomy of the human brain other than very cursory. DTI [diffusion tensor imaging] is interesting but DTI is an approximation. It basically tells you where fiber bundles are [unclear]. It will never tell you about synaptic relationships. That's really one of the major issues.

KD: Let's step back to the BNU. The logic of bringing the three or four fields, neurology, psychiatry, psychology, social work, together seems obvious to you. You started that in the late 1970s or something like that.

MM: Nineteen 1976.

KD: It hasn't taken off. There are very few places—you can count them probably on your hands—that have anything that approximates it. Why do you think that is?

MM: I hate to sound about the old days. That's not a good thing. On the other hand, our fields, everything about medicine, everything about the institutions we work in have become very, very heavily bureaucratized. All this talk about collaboration and so on is really a lot of talk. In fact, the barriers are much tougher to overcome now than before. Departmental boundaries, cross appointments, independent budgets that go beyond the departmental lines, all of these things which I had are obstacles. Then, of course, to do

credit to why people make life difficult for us is the field is simply not very lucrative. It's much easier for a heart transplant team to justify getting all kinds of things and lubricate the relationship by financial incentives; whereas, here… I don't even want to list all the minor griefs that this field has to deal with. So this is why the only salvation is philanthropy that's going to provide sufficient input to protect you from some of these bureaucratic challenges and that's not always that easy to come by.

KD: That's right.

In terms of the good old days, the [unclear] barriers, the barriers of world views seem to have been much greater. The notion that [unclear] treating the brain and psychiatric or behavioral issues was foreign to psychiatrists and the issue of neuropsychiatric symptoms being important for neurologists was foreign… There was little precedent for neurologists to work, I assume, with neuropsychologists. You didn't have it at BCH. In some ways, those intellectual boundaries have if not withered, they've become much less intense. Still, it's not enough to counteract this other force, I guess.

MM: I think these are purely, in my opinion… Today in medicine, really there isn't that much mileage you can get by the intellectual argument to say, "Brain is related to behavior. Ah! Isn't that interesting?" On the other hand, if you can say, "Well, if I'm a neuropsychologist, I'm going to bring in a million dollars more," that's a different argument. The one way to deal with it is have somebody endow an institute and, then, you decide what you want to put together. Maybe you want to put together a philosopher or a massage therapist or whatever. I think it's a practical issue. But, at that time, it seemed clear that we had some elements that we had to take care of and that was it. Occasionally, we would have a nurse come in or a speech therapist would come in, but they never became permanent features.

KD: Do you think that providing multidisciplinary care for patients who have cognitive and behavioral issues is better care and, if so, is there evidence or is it just a strong feeling?

MM: Oh, I think in our field evidence is hard to come by because, now as opposed to then, what behavioral neurology has become if you're [unclear] disease, we're dealing with diseases that are progressively getting worse. So it's hard to know how you would describe. Personally, there's no question. That's why I have fought against all resistance to maintain the same structure in the BNU, which I have here exactly the same way, even more so than before. So I'm convinced there's no question. But would I have…what is it now? Class A evidence? I have no idea of how I would even start to look for it. For example, one area that I have supported a great deal is our social worker system. Our social workers, one of their roles is to develop life enrichment programs. What is the evidence that they work? I don't know. I like that.

KD: You like social workers? You like life enrichment?

MM: Both.

KD: So do I.

Keeping the dementia or the Alzheimer's and the behavioral neurology together, again, it is an anomaly across the country. Most dementia centers are not structured this way. Why do you think it's so important? What are the advantages and what are downsides?

MM: Historically, if you look at, again, the accidents that bring me to where I've been… Initially, stroke was, of course, the bread and butter of disconnection syndromes and behavioral neurology. In fact, in the BI newsletter—in the few initial years where I had just moved to the BI—headline they had featuring me was "He can tell where the lesions are."

KD: [chuckles]

MM: Now, in those days, examining and telling where the lesion was, it was really important. This was a behavioral neurologist's job to tell where the lesion is

KD: You did that by feeling the bumps?

MM: Yes, feeling the bumps. [chuckles] You examined the patient and you said, "Oh, this is it. The apraxia of this… Here it is." Of course, the next year the MR's [magnetic resonance] came up and, at that time, that kind of a job for a behavioral neurologist or the neuropsychologist became ridiculous.

KD and LK: [chuckles]

MM: So, then, stroke changed completely. Blood pressure was still not well treated in those days. There were still people with atrial fibrillation, rheumatoid fever. We saw a first and only stroke in young people, which was the bread and butter of behavioral neurology. Well, now, stroke is an eighty-year old who has a fourth stroke and they are in the hospital for twenty-four hours. Stroke no longer became the bread and butter. So dementia emerged. Initially, actually, my approach to dementia was very negative. I said, "This is the last place where you want to do brain behavior relationships." Then, because of modern imaging, it turned out that while the metaphors and the thinking is very different in neurodegenerative disease than stroke, neurodegenerative disease adds a new dimension that stroke doesn't have. So that's how *I* moved into neurodegenerative disease, but I didn't leave the rest behind. That way, just like you collect garbage in the attic, that's how behavioral neurology and the cognitive neurology thing that I have now is sort of a hybrid. It's a little bit of a lot of things.

KD: It's a reflection of your history.

MM: Yes, like so many other things are.

KD: Are there downsides to this marriage?

MM: I don't think so…I don't think so. No. Even for training, you have to have the fellows exposed to a variety of things. Of course, there's the advantage today in hyper specialization for financial reasons: grants, clinical trials, that sort of thing. Again, philanthropy [unclear].

LK: I have a question. When you were talking about the beginning of the BNU, you said dementia was a rarity and, then, it moved to the forefront of behavioral neurology. I was wondering if you could talk a little bit about how that changed.

MM: I'm sure the patients were all there, but at that time, there was a very comfortable thing as age, senility. We did see a few young ones with neurodegenerative disease. It was rare. They were all called Pick's disease.

It's kind of interesting, because, at that time, I was getting interested in the cholinergic system. I don't think there was any other American neuroscientist, maybe with the exception of Carl [W.] Cotman, who was doing any work at all in cholinergic [unclear]. It was all European and wonderful work, the European. So I developed that system and I discovered the origin of the cortical cholinergic projection in the monkey with Gary. We sent it to *Science*. It was rejected. Nobody was interested. That was 1975. The next year, Peter Davies came and gave his lecture at Cold Spring Harbor and he described the discovery of the cholinergic lesion in Alzheimer's disease. Suddenly, the cholinergic lesions, everybody said, "Oh, Parkinson is dopamine. Alzheimer's has the choline. It's all solved. Alzheimer's in not a disease. Senility is a disease of the transmitter in neurodegeneration." Suddenly, I had so much grant money, I didn't know what to do. I got a McKnight award. I got a [Senator Jacob] Javits Award [in the Neurosciences] for seven years. I, literally, was saying, "Should I give this back?"

LK: Wow.

MM: I had fellows. Then, because there was all this huge advertisement, "Don't think that just because your father doesn't recognize you that this is old age. This is disease. Bring him to the doctor. We were deluged with patients who had dementia. Then, really, I wasn't all that interested in turning the BNU into a dementia center. But we saw our patients.

Then, when John Growden came and said, "There's this [sounds like RFD] from the NIA [National Institute on Aging] about the center. Would you like to join?" Then, we started these remarkable meetings with David [A.] Drachman, John Growden, [Suzanne] Sue Corkin, and I to put together the center. At that time, obviously, our interest in dementia increased and that's where I started to work then on the human brain instead of monkey brain post mortem, and became interested in a different kind of anatomy, neurofibrillary tangles, where they were distributed, how this affected symptoms. Then, there was a better integration of my clinical work with my basic science work. Those were the cholinergic years and they were very exciting. Again, I must say, even if I say so myself, all the work we did then is still today absolutely valid. There's no new

material that's added to the organization that was at that time shown both in the monkey brain through HRP and in the human brain through the availability of monoclonal antibodies, which was a new methodological phase.

KD: You didn't anticipate that the cholinary system would become such a center of focus and so popular. What led you to study it?

MM: Dick Wurtman. When I was taking his course, then one of the things that came up during my reading was that the hippocampus contained large amounts of acetylcholine and, then, there was one other thing. [pause] I think at that time, it was the year when David Drachman had shown that scopolamine caused memory loss. Then, there were some experiments by a guy called [Mark R.] Rosenzweig where he showed that if he put rats in an enriched [environment], their acetylcholine increases.

Oh, yes, then, of course, the main reason is I had received a fellowship to study the septo system. The reason I wrote a proposal on the septo system is because I had gone to a conference at Wayne State University in Detroit [Michigan] where Max Cowan and [Lawrence W.] Larry Swanson described their anatomy in the rat with a septo system. Then, there was some other talk showing again a lot of acetylcholine [unclear]. All these things came together.

Then, there was the opportunistic issue. I thought it would be fun to play around with that, literally. I would go on the weekend and all these chemicals would be…and I'd take a little bit of this and a little bit of that. In the first several experiments, nothing worked. Then, suddenly, the method came into its own, but it was, literally, just fooling around until something worked. It was a lot of fun.

KD: I'll bet. Did you ever think that you could be fooling around for a very long time and nothing would work?

MM: Oh, I would then move to something else. I had done a *lot* of things that didn't work. I had done huge numbers of Frankenstein experiments to be able to study connections in the human brain. I would put human brain in an electric current with cobalt and all kinds of things and it didn't work.

KD: Interesting.

Unless you have a question, maybe this would be a time to stretch our legs and relax. You've been great. It's been interesting.

[break in the interview]

KD: We've covered some of this, but let me start by asking in a slightly different way. What do you think led to your love of neuroanatomy, your passion about it?

MM: [long pause] In medical school, there really wasn't… Well, that's not true. Probably… I suppose I was so much in it that I [unclear] get to that. I couldn't really tell you what… I really think it was this paper I wrote on the hippocampus in Wurtman's course. I would go down to the basement of Countway [Library of Medicine, Boston, Massachusetts] and there was this unbelievable collection, especially a journal that no longer exists. It's a German journal. It's called der *Journal für Psychologie und Neurologie*], big page sizes. There was just anatomy that was unbelievable. I think it was the hippocampus. I read a lot of papers and then the Lorente de Nó's paper, which, of course, was in der *Journal für Psychologie und Neurologie*. Then, to have the opportunity to do this first hand with Gary and Dee, that's when some of the anatomy stopped being rote. I remember… Isn't that [unclear] about the cranial nerves?

KD: Some limerick, yes.

MM: It just stopped being there and it was really fibers that I could trace and I could see. Then, that three-dimensional reconstruction. I got hooked on anatomy. Also, I must say there was a false hope the field had at that time that *only* if we could list enough connections, we would figure it all out, that it was just a matter of finding enough. Then, suddenly, with HRP and autoradiography life became *so* complicated that that hope just wouldn't work.

KD: At the time you started, did people have an estimate on how many billions of neurons our brain is constituted by?

MM: The numbers were there, but I don't think anyone had any notion.

Then, of course, there was a big teaser that came in by [T.P.] Jones and [E.G.] Powell in 1970 ["An anatomical study of converging sensory pathways within the cerebral cortex of the monkey"] and, then, Dee Pandya and [H.G.] Kuypers [Cortico-cortical connections in the rhesus money] in 1969 where they actually used the Nauta method and showed this remarkable thing: primary sensory, primary association, secondary association, multimodal limbic It was beautiful. It was just what Geschwind had described in the disconnection syndromes. It was just a matter of filling in some of the little details, you know, what the frontal lobe was about. Some of the details are very, very… The hierarchy sort of was there but it was not really like the hierarchy that you see in the Ottoman Empire and more likely the American government where it's hard to know who's making the decisions. That's when it turned out we needed things more than just anatomy.

KD: We'll come back to your imaging, but do you think that if your career started, oh, twenty-five years later—I'm not sure I'm doing the numbers right—and our ability to image was available that you might have started there? Let me ask this in a slightly different way. There are lots of young people who are pursuing neurology and neuroscience and anatomy is certainly less popular compared to imaging. It's very sexy and engaging. Have you thought about that?

MM: Yes, I wrote about that. I had a review paper I wrote about the landscape of connectivity. I am worried about the mistaken assumption that the computational approach while you keep your fingers clean is really going to be answering questions about the human brain connections. Having said that, the other way I could answer your question is if I had started my career twenty-five years later, I wouldn't have been able to do what I did because animal research today is *so* complicated. In those days, I must say we did things that we shouldn't have done. We were a little too lax in our approach to animal welfare. I had unlimited access to primates and I did primate work that I don't think I could do today. Primate research has been decimated. There are very few people today that do it. When I was working on it, this was the great days with Vernon [B.] Mountcastle doing single unit recordings and we could relate single unit recordings with connections. There is very little of that work going on today even if you want to.

Then, imaging is too easy. *Anyone*…anyone *anywhere* can do functional imaging. The problem with imaging is that no one realizes how complex things are under the hood as opposed to anatomy where what you get is what you see. In imaging, it depends on what controls you use, how you set up your Gaussian kernels, what general model you use, what toolbox. So by the time you get it to a blob, that's kind of the blob of the blob of the blob of the blob and it depends on the eyes of the beholder what you're going to conclude.

So I think it's very important to train young people into the limitations of the methodology that is being used. Unfortunately, anatomy, which is so elegant in the human brain, is extremely difficult to do in the laboratory. Now, we still have learned a *tremendous* amount, thanks antibodies. So we know the neurochemistry of the human brain in great detail and thanks to the work of some pioneers with retrograde [unclear] a little bit of the human anatomy, but not much…not much. DTI, of course, and resting state connectivity and so on are being used today frequently. I have a lot of respect for those methods. We use them. But from there to try to conclude that what you're seeing is a synaptic connectivity that real neuroanatomy shows, there's a big leap of faith there.

KD: Let's shift from anatomy to your interest in language and aphasia. When did that take hold?

MM: Really recently. I started to see patients with progressive aphasia in the 1980s and I wrote my initial paper. Then, I sort of didn't pursue that much. I had lots of other things to do. Furthermore, Geschwind was the aphasia person and I didn't really want to sort of appear to be either competing or copying, so I took the right hemisphere. Geschwind was on the left side. António Damásio was interested in language. I didn't do research and, then, language didn't exist in the monkey, and I was interested in animal models. Then, when I became more interested in imaging [unclear] the human brain, my interest in PPA [paroxysmal perceptual alteration] increased because the patients that I was seeing so were incredible in their spectrum of symptomatology. I learned new things. I, basically, had to change my concept of aphasiology based on the patients that I saw. So I kept getting more and more interested in these patients and I still am very interested.

KD: How important do you think the first group of patients that you describe, that you happened to see then, was in sparking this or were there lots and you just noticed?

MM: Probably it was the fascinating group and I must say, in those days, I was seeing a remarkable flow of patients with riches beyond belief. I also published half a dozen of people who were possessed by the devil.

KD: Right.

MM: So that was a series. I published Tourette patients. That was a series. Then, there were the PPA patients. It was one of several groups that I found particularly interesting. I didn't realize that this was… In fact, I didn't even understand what all that excitement was about. I mean, language is in the brain, so neurodegenerative disease, why not language? Apparently, that hit a time when everybody thought there was only one kind of neurodegeneration. It was called Alzheimer's disease [unclear] to memory. So this became a novelty and attracted a great deal of interest. But, at that time, this was one of what I thought was paradigmatic patient groups that I was trying to describe: the possession to tell us something about TLE [temporal lobe epilepsy]; the Tourette to tell us something about neuroleptics and tic control; the PPA about focal neurodegenerative diseases. It didn't occur to me, I must say at that time, that this was going to be my main focus in the coming years.

KD: That occurred with the advent of imaging? Walk us through…

MM: Patients. There were just some patients that I started to follow for years. Patients would come. These patients would go to…and the neurologist would say, "Oh, you have a stroke, but we can't see it" or go to an ENT [ear, nose, throat] doctor and "There's something wrong with your voice." So patients started to come and once that initial report came, then more came and we were a referral center. So those patients were a remarkable group of patients. It's the individual patients that we got so attached to, patients who couldn't say a word and who would drive all the way from the middle of Pennsylvania to come to see us, patients who came from New Jersey with a laminated card saying, "I want a ticket to Boston." They couldn't talk. That got me *very* interested in this group of patients and we developed this personal relationship to the patients. Then, that turned into the systematic research program and we got a good deal of funding for that. Of course, imaging helped a great deal. The imaging was clear even in the first set of patients that language is in the left and there was [unclear] in the left.

KD: Have you seen other groups of patients that you haven't written about? Are there still cases possible for neurologists in training and in their careers to observe things that haven't been seen before and use that to figure out a research path?

MM: I think so. There is here something that I hope someday I will have the courage and time to try to make a stink about.

KD: [chuckles]

MM: And that's the discouragement of several case studies. I don't need to tell you—you and I published at least one such case report—that there is a lot to learn. Everything we know about, can you imagine being in neurology without an HM, without Phineas Gage, without [Pierre Paul] Broca's patient, without [Carl] Wernicke's? These were single patients that just blazed the way in what we know about the brain.

Today, this is discouraged. We've got statistics. So what you have is you put the oranges and bananas together and say, "Guess what?" It's a little sour; it's a little sweet but statistically, so and so. I have nothing about statistics but I think that this is going too far. Today, I have a couple of fellows who are really very eager. You know, I'm reluctant to give them… I have just sitting on my desk patients with completely unexpected kind of pathologies and PPA. So I'm thinking, let me give them the project. Well, the grief they are going to be facing. I have four patients. Well, it's going to be not enough numbers. So I think that now that approach comes up with this resistance. You're forced now to go for large numbers and large numbers, no single person is going to get that. So you get large numbers and you're one of thirty-two authors and you come up with some statistics with all kinds of significance and it's a different view of brain behavior relationship. I must say the views Wernicke had, Broca had were too simple, but they surely helped.

KD: Why do you think it's not considered good science to do careful single studies, at least that's the preponderant view?

MM: I don't know. It's the same way that anatomy got decimated at review groups, because it was called descriptive. It was, again, one of these things that's beyond belief. The most descriptive thing is the human genome project. There are no hypotheses. They just go and say, "I want to see what there is." Anatomy was just like that and the funding disappeared. It became descriptive and, here, there's this ethos which I cannot understand. On the other hand, I must say I would *hate* to be at the reviewing end of this and be faced with a dozen case reports that I have to decide is it worth publishing or not. I don't know. Then, you get hit with, well, it's a short communication. In 1500 words, only nine things. Then, you say, "How do I know that this is worth publishing or is it just trash?" But Wernicke had a whole book to write on his patients and that made a big difference.

[pause]

KD: Tell us about the evolution from neuroanatomy, the cholinary system, neurochemistry to neuroimaging. What was it like to deal with people who spent all their time focusing on neuroimaging or [unclear] science?

MM: You know, Kirk, I am *so* fortunate to have been there at the time when these things were just appearing. Of course, there was some of that with xenon inhalation and arterial injections with [D.H.] Ingvar and colleagues. But there were shadows. Then, PET scans

came up and I was left behind. We didn't have a cyclotron. So there's nothing I could do about that as I watched [John C.] Mazziotta and [Richard S.J.] Frackowiak come with these beautiful things.

Then, one day, I get a call from [John] "Jack" Belliveau and he says, "Why don't you come over to Charlestown [Massachusetts General Hospital]? We have an interesting finding you may like to see." And he wants to do it on Saturday. Well, Saturday is [unclear]. So I said, "Okay. This weekend, we will [unclear]." I go down to Charlestown. It has a few people there. The MRI. He puts the patients in. That's the one day where the experiment doesn't work.

KD: [chuckles]

MM: So he gets his flashy checkerboards and there's nothing in the recordings. Of course, six months later, he publishes his science paper which is the birth of functional imagining.

Then, at that time at the BI, we had [Robert R.] Edelman who was the radiologist. So he got interested in this. At that time, we had David Darby and Kia [Nobre] was there as my post doc. We said, "Why not?" We went down there and Edelman then developed EPISTAR, which is the progenitor of ASL [arterial-spin labeling]. So Arterial-spin labeling is based on EPISTAR, but EPISTAR was one slice and ASL is whole-brain. We visualized the frontal eye fields while Kia was in the magnet. Now, she has a *very* unactivatable brain and she falls asleep in the magnet, so it was a real struggle, but we got it done.

Then, I got hooked on functional imaging. When I moved to Northwestern, I actually recruited Darren [R. Gitelman] to start functional imaging here. There was none. Zero. In fact, when I said that my coming here would be contingent on functional imaging, they said, "Yes." But they had misunderstood. They thought I was talking about spectroscopy. So we had to start from zero. We were allowed two hours on a Philips scanner in an out patient imaging department, from seven p.m. to nine p.m. So we would go there, Darren, me, and a technician, and we would put in victims to be… It was very, very slow going. In fact, we had to take a red pen and color the areas that we thought had activated things.

But, then, things developed and there was new technology. We had more time. There were some new developments in functional imaging, thanks to one of my fellows, who is now a professor at Duke, Kevin [S.] LeBar. Kia spent a month at a time here. She would go back and forth. Darren was active. Then, we hired a physicist to join the program. I was really very active in functional imaging to the point where I became president [2001-2002] of OHBM [Organization for Human Brain Mapping] a few years later after [Karl] Friston. This was a major area of activity. I established, at that time, the CBMG, Cognitive Brain Mapping Group, here at Northwestern, which still continues. I am still active. I must say I'm less excited about functional imaging and more excited about

some of the structural imaging parameters, and trying to figure out what in the world resting-state connectivity means.

KD: What do you think it means?

MM: I don't know. I wish somebody would explain it to me…since the coherence between two areas occurs at .01 hertz or .1. There is no biological system that has that time course. So I don't know what it means.

KD: It's interesting that a considerable percentage of the people who are interested in imaging these days are young people. They're focused on resting state.

MM: Oh, it's a toolbox. You push a button and see what you get. This issue, today again, is the beauty of anatomy. You have to start from scratch and do every piece so you know. Step one to step two, what have you done? Here, in a lot of the functional imaging, you don't get that. A graph theory, I think, is the best example of that. *What in the world* do these lines mean? Beautiful map. I don't know what they mean. But, again, maybe I'm just simply old fashioned and I can't see that. I kind of like to see things simplified. In the resting state, the work is *gorgeous* and it has validity, no question. Some of the connections make sense. I wish I had more knowledge about the physiology.

KD: The networks that are imported don't make sense to you?

MM: Oh, of course not. You see, today, the word network is used in a completely different way. I used network in a very strict way. It had to be monosynaptic connections and coactivation in the given domain. Today, network is like Facebook. Basically, if five areas all light up when you're doing X, it's a network. That's really more like cohabitation than a network from a synaptic point of view.

KD: How do you think the story is going to end up?

MM: Oh, beautifully, like everything else. I'm sure that someone is going to come up with something that realizes it's not on [unclear] but on something else, something that is more closely related to neuro function and that combines spatial resolution with temporal resolution and, then, draws it back to anatomy.

Now, I must say, this is not just more data. This is just data that's not like the platonic cave shadow, but closer to reality. In fact, I'm not sure more data is useful. I would like to pose the following problem to a neuroscientist to say, "What if you had a method where you could put an electrode in every one of 40-billion neurons in real time? What would you do with the data as the animal did various things?" It's not clear to me what you would do with it.

KD: How are you using functional imaging to advance your understanding of language functioning, other cognitive functions?

MM: We use functional imaging, the real fMRI, the resting state of MRI, [unclear], DTI. All of these things we use and we do all the right statistics. My interest is to see what picture emerges. There's never going to be… I shouldn't say, "Never." But right now, it's not possible to say what's the *real*…real truth about brain function, so we come up from different approaches and try to see how we can hone some of what we know just a little better and compare it to thirty, forty, fifty years ago, or even beyond, where each step was big. Right now, the steps are very, very small because you're building on already a lot of knowledge. So one has to be more patient. That's why, you know, when you discover a new gene for a disease, it's instant fame. You've done a quantum jump. But when you try to figure out how do you name an object, the increments are very small. At this time, the question that I'm focusing on most is just that: How do we understand the meaning of a word or use it to name an object? I can tell you that still there are a lot of questions there and the new insights of the increments are very small.

KD: Having participated in a time of science where there were huge leaps because very little was known or the tools were limited, what's it like to go from that experience like tasting the best wine possible to having lots of wine but it's really hard to discern the differences?

MM: I like the challenge a lot. Then, again, we're dealing with these PPA patients. This is really a remarkable set of patients because as opposed to a stroke condition where you have a huge piece of brain taking out the circulation at once, you have here a slowly progressing short circuit through different parts.

[break in the interview]

MM: What was your question?

KD: Can we play it back to me?

LK: Sure.

[break in the interview]

MM: Atrophy spreads in the brain, so we have the changes in language. It's a different dimension that we are able to look into. It's been, for me, very interesting. So to answer your main question, I think there is a *tremendous* amount of new discoveries that are out there, not to erase the past and to put the new information instead but to take the past and, then, to see. It's like iteration when you try to find out some square root of something, to just find out in what way you can improve what has been said before—unless, of course, the past had some main error. I think it's more challenging than before. This is why we see now so few individuals coming out as pioneers. Things are large enough that they require large-group approaches, so that makes it even kind of more challenging to establish a career.

KD: Sure.

You had mentioned that you're finding the structural imaging to be more informative or at least closer to meeting your goals. Is the structural imaging of the atrophic pattern or what did you mean by that?

MM: I really shouldn't say that I like any method more than any other. It's just that atrophy is a statistical visualization of the thinning of the cerebral cortex compared to a normative group. The interpretation is simple. If you believe that the segmentation is correct, that the [unclear] differentiation is done right and this is done with editing as well as with toolboxes, then the result is simple. You say, "This is thin." So the reason I highlight structural imaging is because the interpretation doesn't require leaps of faith. Now, we use all the other methods as well, but atrophy morphometrically determined has a virtual simplicity. That's all.

KD: If you could go back to visit yourself a few decades ago and you were told that advances in our understanding of the field of behavioral neurology would be associated with neurodegenerative disease, what would you have thought?

MM: Uhhh… I think I would tend to dismiss that. That was not the ethos at that time, neurodegenerative disease. After all, we were all after that ideal lesion. It would be small enough that it would adjust that given [unclear] and to deal with a disease which is, at best, spread well beyond a single focus.

KD: Yes.

MM: This is why gunshot wounds really didn't get that much traction, for that reason, and that's why a stroke was the gold standard for quite a while. From that point of view, I would have dismissed it and, now, it turns out that there were some major problems with the stroke approach, which the neurodegenerative approach is sort of trying to look into. Of course, the main thing is fibers versus cortex.

KD: Yes.

In thinking about your work, we've talked about some of the methods that you've advanced, some of the systems you've looked at. Are there three or four papers or areas that you would highlight as being the most meaningful to you or, perhaps, if there are different ones that might have the most impact on people's understanding of how the brain works?

MM: Well, I think that's relatively easy since these are the papers that are the most cited. Really the cholinergic story started with my 1983 paper ["Cholinergic innervation of cortex by the basal forebrain: Cytochemistry and cortical connections of the septal area, diagonal band nuclei, nucleus basalis (substantia innominata), and hypothalamus in the rhesus monkey," 1983] on the monkey cholinergic system. [chuckles] Basically, no one has ever attempted to replicate it, so I don't know if it's right or wrong, but it was the

totality of connections of the nucleus basalis in, I don't know, three dozen monkeys. It was a long paper.

Then, the spatial attention, the 1981 network paper ["A cortical network for directed attention and unilateral neglect," 1981]. Actually, it introduced the network idea in the sense I use it. And there were some theoretical papers on networks and the sensation to cognition.

Then, the PPA paper, the original one ["Primary Aggressive Aphasia: PPA and the language network," 2003] in the *Annals* paper.

There are a couple of papers maybe that are not as well known and one of them is my chapter in the frontal lobe book [*The Human Frontal Lobes: Transcending the Default Mode through Contingent Encoding*] by [Donald T.] Stuss on contingent encoding.

Then, another paper I like a great deal and I don't think anyone else has ever read. That was one [unclear]: Geschwind would get a lot of these requests to write chapters and so on. [chuckles] So one day he said, "A neurologist needs a chapter for the North American Clinics of Neurology. Would you write a chapter?"

KD: On delirium?

MM: Yes, on delirium. I think it's a very good paper and I had a lot of fun researching it. But, it was in an obscure journal, not really related.

So I have several papers that haven't, I think, received the…because of where they were, including a textbook of ophthalmology on visual syndromes [title could be entered here]. So there were things that got lost.

KD: You published two editions of *Principles of Behavioral* [*and Cognitive*] *Neurology*.

MM: Yes.

KD: But you haven't revised it, to the best of my knowledge since 1990 or something like that.

MM: Two thousand is the last.

KD: But that's a long time ago. Why not?

MM: [sigh] Uhhh… Well, one, because I'm lazy and…

KD and LK: [chuckles]

MM: …two, because I've had a lot of other things in between and, you know, third… [pause] Maybe I shouldn't say it but it's becoming increasingly more difficult to find

authors who can write papers not like this but like this [perhaps, clarification is needed here to note to what Doctor Mesulam is referring] and to have the broad view. My book, as opposed to many others, does not have short chapters. I tried to find people who could address a field as a whole and not write one on Gerstmann's syndrome, one on this, one on that. It's very difficult to get that kind of a chapter. Furthermore, I also made the mistake of writing four of the chapters and that's a big burden. So if I were to do another revision, I would write fewer chapters. I would keep the first chapter to myself.

KD: Do you think it's harder to find people to do these broader kinds of chapters [unclear] synthesize fields because people have become so specialized, because people are too busy to write chapters?

MM: No. They don't want to sound like [unclear] doing things, generalizations that no longer… When you have the authority of a Damásio, it's easy to say, "This is this." But, today, if you want to keep your funding sources and your credibility, you don't want to say generalizations that are just very difficult to sort of accept, because, now, every one has reduced it to its primary ingredients. Once you do that, then you need to write a whole book on any given topic. So it's very tough to sort of have the courage to say some things that are integrative in a major way which is useful to the young people who are getting into the field. You don't want to feed them the wrong food at the same time that it's credible to your colleagues. I think the times have changed, that it's more difficult, for good reason, to do that. I think twenty-five years ago, I could have written a chapter on the connections of the frontal lobe. I don't think I can do that today. I mean I could but it's just going to be like… In fact, if you look at the websites on connections, sure, page after page, it lists, you know, fifty-nine references.

KD: You have been very skillful at synthesizing broad fields and providing pillars to sort of understand how things work that have been very, very helpful. Are you, at this point hesitant to do that because any one thing you would say or any example would have counter examples or people who are *in the know* would say, "Well, that's too simple," or "He doesn't get it?"

MM: I don't think so, Kirk. I really don't think so. I look at it this way. [pause] Well, I really do want to do another and maybe all of these are excuses.

KD: [chuckles]

MM: You know, I've had interesting experiences and some chapters were very, very difficult to find authors. But, that, I think is an excuse. I do want to do that.

KD: I guess I'm resonating to a broader challenge. There is so much knowledge and there are so many details that if you want to be helpful and provide a broad outline of understanding, which I would say very critical for young people and people who are not experts, you run the risk of people who are experts being critical in a way that…

MM: There is no question that that's really almost totally unavoidable and it happens today. You see it in the review process of papers. I don't think that there's anything that you can say other than just mere numbers and facts that you wouldn't have someone else say, "Well, I don't think that way," for, probably, legitimate reasons. I think this is true in every area. You can look at aphasia, frontal lobe, parietal lobe, limbic, memory. Just look at memory. It was very simple. You took the hippocampus out. You were amnestic. Now, how many types of memory are there and each one with a different anatomy? If you don't take that into consideration, I think that's a [unclear].

KD: But if you want to introduce a topic to people…

MM: It can be done. It really can be done. The reason that I wrote the book was out of self defense, because you know I was giving the course.

KD: Right.

MM: By the time I decided to take on the book… [pause] I forget how the book came. I think it was through Fred Plum—yes—who was an advisor for the series and, then, they asked me. The problem was I was giving a lot of the lectures—I think maybe six, seven—and there was no text. Then, it's interesting because I was given a topic: X, Y, and Z. Well, you can't possibly master seven different topics in behavioral neurology, so there was a lot of a liberty that I took in putting things together. So, suddenly, the book made a lot of sense, because I would be able to have something in writing that would kind of bring this up. I would refer to it and so on. Now, it's interesting: no such course exists. The course that *you're* giving, which is *very* successful, has a focus but it is different. Even though you do that as you introduce your subject, that's not the focus. There are no such courses left, not even in the AAN. There is no all behavioral neurology. It may be that we've gone beyond that.

Bu the challenge is still interesting. I would do the book again, really, if I had the time where I wouldn't have so this is due, this is due, and so on.

KD: Sure.

MM: I haven't given up by any means on a revision. In fact, what I'm considering is whether it should be two volumes. Really, the one volume, which is *completely* out of date, is the one on neurodegenerative disease. It's because, again, I had the least amount of interest in that at that time. That needs complete revision.

KD: Do you think that our field has become so super specialized that it's very hard, if not impossible, to have a broader view of the overlap or how things fit together?

MM: Some of the main themes are… [pause] I think if you look at the behavioral neurologists today, it's not so easy and I think for good reason. You can't show that neurodegenerative disease is the same thing as a stroke-caused neglect. There is no Wernicke's aphasia in neurodegenerative disease and so on. So their examples are less.

They deal with more complicated things. But, I must say that the clarity of these domains, of these five networks, prosopagnosia, this, this, and that, while we can teach it, it's less easy to demonstrate in practice.

KD: What do you think are the advantages of doing a neurology residency in trying to pursue cog [cognitive] neuroscience or trying to understand any of the things we've been talking about? It's a big commitment.

MM: It's a huge commitment, but there's no other way. Cognitive neuroscience, of course, has absolutely *exploded* because imaging…principally because of imaging. But there is no patient interaction. It's not enough to say you've tested patients in the magnet. You have to take care of the patients and do the initial diagnosis to understand what is going on. There's no substitute. That's why I still see patients. On day a week, I'm right there and I'm doing a diagnosis. I don't do pronouncements. I spend my time and I obsess about details. This is this. This is that. It keeps me honest. Without that combination, which only a neurologist gets, that…even though, again, it was part of a team.

KD: It keeps you honest in terms of being grounded in real people or keeps you honest in terms of humility? What do you mean?

MM: Oh, no, no, no. It tells you what your reality is like, that life out there in the clinic is not simple. Every time you find out a patient has memory loss, well, it's not an HM. It's a little different memory loss. Then you test it fifteen minutes later. Well, maybe it's different. Ribot's gradient is not all that clear and so on and so forth. So only struggling through this in the clinic is going to show you what you're really dealing with.

KD: One can imagine a junior or senior coming out of Harvard College many years after you who wants to add to the literature and has to balance spending eight, twelve years going through medical school and residency before having their time open up to address some of these issues versus getting a Ph.D. and starting at age twenty-two. What's the advantage, if any, of the road you traveled?

MM: People become monks. They go to monasteries. They climb Mount Everest. They do all kinds of things. I don't know why people choose certain careers. But, there is an ideal that one has about certain things they want to see themselves become. Then, they make a decision about the trajectory of how you go there. There are so many variables from the financial to the logistic to the standards, so everyone needs to come up with a very personal decision. It's a testament to the human brain that you can make so many decisions which are *all* in their own way perfectly correct.

KD: I assume that when you see patients, you allot time to spend with them and to think about them. I know when I started, we used to bill by the half hour slots. I'm not sure how kosher that was or not, but it was this awesome opportunity to spend two hours. The world has evolved, or medicine, so that people are given very little time. It sounds like the solution that you have found for yourself is philanthropy to sort of provide that space.

But what other options do people have in your view not to have to rush through this process, which is counterproductive to everything that you love to do?

MM: I give my fellows and everybody in the clinic, the MDs, an hour and a half for a new patient, which is not exorbitant, but not short. Yes, we subsidize by philanthropy and endowments. I don't know what the answer is. That is definitely another major challenge in the field as a whole and I don't think that's going to get any better. Yes, I don't think that's going to get any better, so the only thing I would say is you need to have even more of a pioneer spirit to take the challenge that this is the way it's going to be and try to be creative about how you're going to deal with it. But for training, short patient interactions, that's the problem.

KD: Right. It's a big challenge.

Let's shift… Actually, let's look at a couple of the transitions in your career. You moved from Boston to Chicago in 1994. Can you tell us a little bit about the context of that move, how difficult the decision was, what your expectations were? It was a big deal.

MM: Well, it was a huge move. I would say, in part, traumatic. Some things sort of stayed the same in some ways, but, also, everything changed. Geschwind died in 1984 and there were many years there of interim and things started to get difficult administratively, to the point where there were some issues that you're well familiar with that made it intolerable to continue the status quo. So there were some big decisions that had to be made. There were some local options but that didn't allow the full continuity of the existing unit. Also, it became clear at that time that every one in the unit would be well taken care of either by having the option to move to Chicago or to find adequate positions for careers in Boston. When that became clear and Northwestern put together a very major package with the job to start in Alzheimer Clinic and functional imaging, then, the decision was made, tremendous, the most difficult decision I've ever made. That's when the move occurred. There were many, many details that I'm not sure are relevant related to the move. There were a lot of people who were missed, though invited to come. That's how we started things here, initially slowly and, then, they grew. I still wish that things in Boston had worked out well, but not having done so, my great comfort is that every one who was with the unit has really flourished and that what we started here has also flourished.

KD: In terms of lessons learned… Before I came, I was talking to my fellows. It's very easy to look at people who are senior and think everything went smoothly and, yet, they're not sure what's going to happen to them next. Reflecting on these really important transitions where it wasn't part of a game plan are there certain take-home messages or things that you learned that would be helpful to others who face transition and great uncertainty?

MM: [sigh] Uhhh… You know, there's really no magic. I don't think I want to say things that are too general. The only certainty is that there will be a lot of uncertainty in

people's lives. Sometimes, people are lucky. I consider myself very lucky in circumstances that were really critical where things turned out well.

KD: When you left, were you mostly optimistic or mostly anxious?

MM: Oh, there was a huge amount of anxiety. For a long time, things here, there really was nothing. Northwestern is one of the most rapidly growing medical schools. It's now very respectable. When I came here, it was very, very little. As I told you, functional imaging was rudimentary. There was no Alzheimer's. There was no clinic. I had to start the clinic again with the usual resistance. Why do you need so many people to see so few patients? Then, things were fine. My first application for an Alzheimer's center was funded. Five years later in the [unclear], we got the highest score in all of the centers. This last review, we got a perfect score. No other center has ever received such a score. We got our PPA study funded. There is young faculty who are flourishing. Fellows, especially recently, are really topnotch. As I told you, there's a proposal to double our space with new areas, so things have worked just fine. But, again, it's because of other people who were willing to join the enterprise. But none of these things are predictable. In retrospect, I can't tell you did I do anything right. It seems like I didn't do any *major* mistakes. Things worked out. It's thanks to all the people who contributed. If you put together this and that, large numbers of people came through and are now here.

KD: Around 2000, as I understand it, the relations were restructured so the unit was reporting to the dean and not to the department. To the extent that it's possible, describe that transition and how that came about and what the benefits were.

MM: From the very beginning, I—like anyone else, I'm not original to have independence, of course—really never wanted to be department chair because I'm very focused, but I wanted to make my own decisions. One way to deal with it would be to make the Center outside of departmental control. I lobbied for it for a number of years. Finally, when [Lewis] Lew Landsberg became dean here—Lew was, of course, a former BI person—he saw the wisdom in that particular structure. That was also at an interim time when neurology was looking for a new chair, so there was the right kind of window without having to go into a lot of fights.

KD: Sure.

MM: He, then, changed the structure in that way, so now I have a completely independent budget. This is our space. We still deal a lot with department circles. I can't give primary appointments, so I need to deal with departments for primary appointments. I wouldn't say that it has absolutely no wrinkles, but I'm quite satisfied with the way things are now.

KD: Are there other groups who were in the department who followed this path so that they, also, are directly reporting to the dean?

MM: No.

KD: This is unique?

MM: Yes.

KD: Moving from Boston to Chicago, you shifted the name from the Behavioral Neurology Unit or Center to the Cognitive Neurology Unit. Why did you do it and what's the difference?

MM: I thought at that time—that's one expectation that didn't turn out—that I was actually going to turn it into a department of human cognitive neuroscience, that, basically, we would do that. We would have a clinical enterprise. It would be called the Behavioral Neurology Clinic and, then, we would be a functional imaging outfit with some other things, ERPs [event-related potentials] and so on. That really never materialized. I was not able to obtain faculty appointments for Kevin LaBar, for Kia, for Tobias Egner. They came in and when the time came to give them an appointment, no clinical department was willing to do it. The Basic Science Department in Evanston [Illinois] wanted their piece of flesh. Why should I give an appointment if he's going to be here? It didn't work out. That was the reason why I named that. I wanted to prepare the groundwork for that.

KD: Do you know why the field was named behavioral neurology and not cognitive neurology and who actually came up with the label?

MM: I really think it was Geschwind's. I think he wrote a paper about behavioral neurology…yes, either with Frank Benson or with this psychiatrist. I forget his name. I think it was Geschwind. I don't know why he chose the name behavior, because, clearly, behavior was not the focus of the disconnection syndromes. It was much more cognition than it was behavior. But that's the word he used. He *specifically* in his letter talked about *the Behavioral* Neurology Unit.

KD: Behavior was more measurable than cognition at the time?

MM: I don't know. I think the word cognitive maybe kind of smelled musty. At that time, it didn't happen in clinical. It was more like a psychology departments. Jerome Bruner was cognitive and he definitely was not disconnection syndromes.

KD: Right.

You have held views about major illnesses that were not the dominant view. One example is your longstanding questioning of at least the core, pure amyloid hypothesis for Alzheimer's. At this point, tides are shifting and there's a lot of uncertainty but, for a long time, you were a minority voice. I'm just wondering if you could speak to what that is like. What are the risks and what are the joys of holding your own ground?

MM: It's interesting that you ask that because I forget who it was but one of column writers of the *Wall Street Journal* wrote an editorial column about how difficult it was in this field of Alzheimer's disease to get funded if you didn't work in the field of amyloid. I wrote her back a letter to say, "I don't know why you say that. I have *never* published a paper on amyloid and I'm fully funded. I've never had any problems with Alzheimer's disease." She didn't write back.

KD and LK: [chuckles]

MM: I really have had no problems at all. I must say that all the colleagues I've dealt with, we haven't had any acrimonious debates of any kind. They understand what I mean. I think the arguments are there. I actually haven't had any… I enjoy the controversy. I must say that, right now, it's becoming less of a controversy. It's just common knowledge that not everything is well in the amyloid's field. On the other hand, we're stuck with it and we better take a leap of faith and act as if that was the answer until we all decide it is not.

KD: What is it like to be involved in academic disagreement? Another example is—again, what's interesting is that over time, these things sort of work themselves out—primary progressive aphasia. You used to debate about fluent and nonfluent and what it meant and were you talking about the same things. Was this Alzheimer's? To what extent did you feel you needed to hold your ground? Was this fun? Was this stressful, these kinds of arguments?

MM: Initially, it got more interest than I expected so I was kind of flattered. Then, it got lost in the shuffle. PNFA [progressive nonfluent aphasia] and SD [semantic dementia] came out and PPA was lost. That's where the puzzle maybe comes out.

KD: The name?

MM: Yes. Basically, David Neary, who I know well and I respect a great deal, did, again, this business of committing…committing to describe the subtleties of syndromes and they carved out this field into behavior, progressive nonfluent aphasia, and semantic dementia. PPA was gone. Now, I thought this was a big problem because the names didn't make any sense. First, I do my best to avoid using the term semantic. I think it basically obfuscates thinking because anything is semantic. Secondly, the person, when he put progressive nonfluent aphasia, gosh, the best example is ALS [Amyotrophic Lateral Sclerosis]. There are *lots* of progressives. Primary was the main issue, which was not there. So there were *years* where I simply suffered the fact that they would be publishing things calling it PFNA. Some others were publishing calling it PPA. Then, the real…and I give credit to her, Mary [Maria Luisa] Gorno-Tempini, who came up with her paper and really *that* was, I think, the point where it became clear that PNFA and SD by themselves don't do it. This little fellow, logopenic, suddenly said the umbrella should really be PPA and not that. Then, the tide shifted and, now, I think no one talks about PNFA or SD. At least those who do are not going to do it in a few years.

KD: But people distinguish variants within PPA.

MM: Yes. I resisted that for many years, but, right now, I have to pay lip service to it, so we do it. For example, now I'm writing a paper where in the methods I say, "I have seventy-two patients. They have this and this and that, but from here on, I'll not mention subtypes, because that's not of interest to me looking at the distribution of atrophy." On the other hand, in terms of neuropathology, clearly those subtypes are useful.

KD: Yes.

MM: Then, again, we have other… It's like BI saying that my value was to tell you where the lesion is. I think today figuring out if one has logopenic, it's not going to cut as a biomarker. You betcha they're all looking at CSF [cerebrospinal fluid].

KD: That's right.

Okay, let's shift to teaching and mentoring. You've been doing it for a long time. In thinking about it, how would you say that has evolved over the years as you've gotten older and have been doing it longer?

MM: [pause] Teaching… There was a course. There were rounds. But the real teaching was the fellows. I have been blessed with incredible… John Tellers. Then I think it was Bruce [Miller?]. Then [Ronald C.] Petersen. Then you came. [Geoffrey L.] "Jeff" Ahern. David [sounds like Dob-ee]. Thomas Hanson, Darren. Yes, this is *incredible* and *many*. You, a professor at Harvard leading the behavioral neurology program. Ron at the Mayo [Clinic]. Bruce doing his [unclear]. John and Geoffrey Ahern….just leaders in the field. Darren just moved to Advocate [Medical Group] to start a behavioral neurology memory clinic. That's the clinical. In basic science, I have Elliot Mufson, who is a professor and now moved to Sun City, Arizona. [Deborah C.] Debbie Mash, who runs the brain bank in Florida [UM Brain Endowment Bank]. [More-ah-ten bray] who is head of Alzheimer's in Turkey. John [F.] Smiley who came here. Nathan [S.] Kline Institute. Changiz Geula was a professor here. Those were just some. Bob Morecraft is still very active in neuroanatomy. [Nathan R.] Nate Selden is now a pediatric neurosurgeon. Then recent ones here… Hyung[Sub] Shim in Iowa. These are not cited like you cite papers [unclear]. To me, this is probably the single most important product for all the years that I've spent.

You know the beauty about teaching is that it's not the giving that is important as the taking by the people that you teach. If you have the trust of the persons you're training that give you the benefit of the doubt and take what you're saying, at least respectfully and, then, reach their own conclusions. That's a rare privilege. I was lucky enough to have that in so many people who came by. Also, residents…residents that I had. There were some special resident classes. I think the last year I was at the BI was a special class of residents. I still have a book signed by all of them. Those were wonderful years.

KD: You had described how important and how generous mentors were when you were at the Boston City Hospital. Did you, at the beginning, channel their approach when you were dealing with people? Did you hear their way coming from you then?

MM: I don't know. Every one has a certain style. I think I was generous with ideas and with providing opportunities and, sometimes, getting involved…well, I was always involved in the research. I think I was but there's no question that I had pretty strict expectations of what people were supposed to be doing and learning. So in some cases that didn't resonate well; in others, it did.

KD: Your approach to the people who were either doing anatomic or more recently functional imaging training versus clinical, the same basic approach or a different approach or mission?

MM: It changed, Kirk. At the time of anatomy, I had done all of it, so when somebody came to me with a slide, I knew everything about that slide. I knew the name of the animal, what was injected. I was there. I knew why it was cut. This is now not the case anymore. Today, when somebody goes to the MR suite and they do…I'm not there. I get the results and I get involved in the interpretation and quality control to say, "Is this likely so and so?" It's a different level of involvement.

KD: Do you miss the other way?

MM: Oh, sure, of course. I still have this… I am actually a laboratory person. I like tinkering. I don't know what would have happened if I had had the time to tinker in the MR suite, for example. I think I would have had a bigger influence on how things were done—for good or bad.

KD: [chuckles] I like that image earlier of applying what [unclear] your brain specimens seeing what would happen.

You mentioned the triumph of having uninterrupted NIH ROI [Research Project Grant] funding, which is an amazing feat. You've also watched NIH change over the years in terms of where the funding levels are and what kinds of things are being supported. What's your sense of the arc of this process, especially for young people who…the rates are really low?

MM: Yes. When I think of my first three or four grants, they were on areas that didn't exist elsewhere. So somebody took this… Today, you can't. Today, it would be suicide. You can only apply for what you've already done in a very established field and proposing things that would *not* generate much controversy.

KD: But, a big deal is made about innovation and that's lip service?

MM: Yes, I know, but there's a lot of this thing: innovation within bounds. If you were to propose something that you had never done before, by definition you're out of the

running. They would say, "What's the proof you can do that? And if you've already done it, then how is it innovative?" and so on. That's where grantsmanship comes in. The grantee is a different vocabulary and you just have to know what you're expected to say. You can't even pretend to be innovative by debunking what someone else has done, because you will be reviewed accordingly. But, I must say despite all of this limitation in the system, *in general*, it has done well. You can't fund every one. Probably…not probably, the United States is the envy of every other country in supporting research. So I'm, again, very thankful to the NIH, even though we all know there are quirks and challenges and also decisions that are not right. For years, this business of not allowing a second revision was insane. This now is rescinded.

LK: A few times you've mentioned philanthropy. I was wondering if those sources are largely from individual philanthropists or from disease-based organizations, patient groups, or even corporations.

MM: They are all individuals and, in many instances, these are people whose family members we have taken care of and who have come and very simply said, "Can we get more involved in what you are doing?" I have an advisory board that's very active. Made up all of individuals with one exception. There's a foundation which was funded by two, a husband and wife, the Davee Foundation, which is where my professorship comes from. They were instrumental in getting the initial package that made it possible for us to move.

KD: How many of your philanthropic folks have put clinical care as a high priority as opposed to either clinical translational research or research in its more basic sense?

MM: To a lay person who is really enlightened and really sincere about helping, the word research doesn't really mean what the word research means to us. Research does not mean just test tubes and a laboratory. Research could be a new way of a clinical approach. It could be a life enrichment program development. So we have used the term research in the broad sense and philanthropists have had no problems with that. But there are some individuals who are very focused, very directed. Then, we honor that party. For example, we know we have a person on our advisory board who raises funds *only* for PPA.

KD: Right.

MM: That's where the money goes.

KD: We're getting toward the end.

Could you talk a little about what it's like that one of your major collaborators, Sandy Weintraub is also your wife, the advantages, challenges, your model of marriage?

MM: First, let me get the challenges out of the way. Clearly, we have to separate family from work. So our offices are as far away from each other as possible, from one end of the hall to the other end of the hall.

KD: [chuckles]

MM: Then, I need to deal with the issue of nepotism. She's the one person whose salary I do not control in any way. Then, she needs to be extra good to make sure that through her achievements she doesn't get into the issue that I'm protecting her in her advancement. We've done that. She has her own sphere of influence. She's the president of INS [International Neuropsychological Society]. These are outside of my influence. The advantage, obviously, has been that neither one of us is very imaginative and we really are very work oriented. We've had Provincetown [coastal resort town] for all the years we were in Boston. We have Saugatuck [Lake Michigan shore resort] here. What do we do? We go on the weekend and we work. So we have a chance to talk about work at that point. It's been a collaboration that's been absolutely key to… I don't think I could have run the clinical enterprise without Sandy. There have been a lot of clinical science areas where she has played a major role and, even in the other areas, her input, even though it's under the hood, has been very important.

KD: Do you ever escape from work? Is there a value, actually…? Maybe I'll say it differently. Is there a value for someone like you or someone's brains, in general, to not work?

MM: Well, Sandy and I have learned to compartmentalize. So we go to a conference in some exotic place and we take time off. That bird you see there is something we saw in Brazil just a month ago. We just take time off. But, would it have been different if she was an investment banker or whatever and, when we took time off, there was no contamination? I don't know. I really am very work oriented. So when I go away, my thought is about something related to work—unless I see a scarlet ibis and, then, I think of something else.

LK: [chuckles]

KD: The distinction between work and play in your case seems to be obscure. You describe coming to the lab and playing, actually. Is work still playful?

MM: Yes, yes! In fact, that's a good point. My childhood hobby was photography. I used to have a darkroom when I was in high school. So what do I do? I come to a discipline where the major thing is to take pictures through microscopes. That's the evidence. Yes. I really do like… This is why my colleagues, it drives them crazy because they come up and say, "Here is the data." Well, that's just the beginning, because, you know, you start to tinker and say, "Maybe I should [unclear] this way and that way." That's the play part. Otherwise, things would be just too [unclear],

KD: It drives them crazy because they want to be done?

MM: Done!

LK: [chuckles]

MM: Finished! And you say, "Wait a minute."

KD: You teach them how to play in the sandbox.

MM: [chuckles]

KD: Other hobbies beside photography that you really enjoy?

MM: Photography is my main. Photography brings with it, of course… We've become sort of nature fanatics and we do bird watching, so this is part of my photography outlet and I do a huge amount of reading, pleasure reading.

KD: What kinds of things?

MM: Oh, all kinds of things. I sometimes read two, three books at once. What am I reading now? I'm reading a book about Florence Kelley in Chicago. She was a social worker. Then, I am reading a book about the filthy rich at the turn of the century, the Catskills and so on.

KD: This is not this century.

MM: The other century.

Oh, I just started to read *Lord of the Rings* for the second time.

LK: Ohhh.

MM: Then, I have a book on the shelf by this guy who wrote—what's his name; [Alexander] McCall [Smith]—*The No. 1 Ladies Detective Agency* in Botswana. I'm reading that. So this is what's on my reading list.

KD: When do you have time to read?

MM: Well, I have lots of hours. I go home and I'll be home by seven o'clock and, then, I read.

KD: You don't work?

MM: No. At home, never. [unclear]

KD: But you work on weekends?

MM: Yes, during the day. Like [Ernest] Hemingway, he used to in the morning put himself four hours to write. That's it. So in the morning, I can write. In the afternoon, I don't write. If I don't write in Saugatuck, there isn't much else to do.

KD: Really?

MM: Here, I am, of course, deluged by [unclear] detail. It keeps me busy all day.

KD: Sounds great.

The future… What advice might you give students, potential trainees who are interested in neurology and cognitive behavioral neurology? What do you tell them now? You described them as needing to be pioneers, but…

MM: Again, I think it is certainty and change. Things are going to change. Nostalgia is not going to be the issue. Every one has to find where they fit in current reality. It's going to change what your expectation is and what you think is valuable. For behavioral neurology, you have to choose a weapon. What are you going to use. So you have to be good either in imaging or in some other basic field to link to what you see in the clinic. It could be genetics. It could be any number of things. If you want to go back to the issue of brain behavior, then today, the weapon is functional imaging. There is absolutely no question about that. Functional imaging has the brightest future. We're *just* at the beginning of functional imaging. I don't think one could go wrong specializing in that area.

KD: If you were making predictions, where do you think the field of behavioral neurology is going to be in a decade and where do you think Alzheimer's is going to be, the field? We'll start with behavioral neurology. What are the biggest things that are on the horizon or the distant horizon?

MM: The customer mix is going to change, so [unclear] stroke. Neurodegeneration is here to stay. Lots of new forms of neurodegeneration. I think we'll find out some things we call psychiatric are actually neurodegenerative diseases in the real term. Head trauma is going to become increasingly more a part of the mix. On one end, we'll have to deal with the end of life. The body is a biological system and so it's subject to attrition. This notion that if you could take away Alzheimer's disease, everybody will be immortal is not really realistic. We have to, then, deal not just with aging as a disease but aging as a stage of life. How do we understand changes that occur because of age alone and not because of disease? That's going to be another important field that I hope behavioral neurology can own.

So there's plenty to do for young people who want to get into this field. What if they happen to want to be just good old clinicians and just see patients? They can do that, too, because I think one can make a living just seeing patients who complain about their memories. Someday, there are going to be real interventions that are going to make the

difference both pharmacological and non-pharmacological. That's the way things are going to change. You can become a good doc and treat or intervene or you can become a scientist and choose any one of the biological fields to pursue the question of brain function. Compared to the function of the gut or the heart, the brain is still challenging.

KD: Do you think that we will have effective treatments for the most popular degenerative disease, Alzheimer's, in our lifetimes?

MM: I have 20,000 slides here. I've looked at a lot of brains. I really think the Alzheimer's changes are almost inevitable, so the possibility that you could delay them further is the real possibility. If you shift curves a little bit to the right, then that will be fantastic treatment until our life expectancy is 120 [years], in which case, there will be a second struggle, but it will evolve. The other neurodegenerative diseases are technically easier but, if you look at things like ALS where you would think that something should have happened, it hasn't. So, we've got a lot more homework to do to understand why cells are failing, why they are failing where they are failing, and whether there is meaningful… Parkinson's is another excellent example. Everything seemed to be clear and, now, nothing is clear. So there's a lot of work to do.

KD: But you're upbeat about progress?

MM: Yes! I think that I can say with certainty that there is going to be progress.

KD: In terms of the Alzheimer's, the delay of onset, which epidemiology studies are suggesting, is already happening, at least the last wave of them. But do you see people who are suffering from the onset having more opportunities for treatment in, again, the next ten year, twenty years?

MM: I am sure there are going to be… Once the disease is there, as you know, things have gone too far whether you can slow progression. In the beginning, of course, we were all [unclear] for studying if we can stop things. Wonderful.

KD: Sure.

MM: I am sure there will be progress in all of those areas, but is it around the corner? I don't think so. I think that there is a lot of rethinking that will need to be done. I am *absolutely* certain there will be progress.

KD: Do you think you're going to retire ever?

MM: Well, of course, I hope. Right now, I cannot figure out what else I would do. I still get my adrenalin from what I do in the work. The question is slowing down sort of like riding on a bicycle. There's a certain speed you need in order to stay on your wheels. But definitely. I have different scenarios. I could spend more time outside of Chicago. So there are scenarios that Sandy and I have considered. But right now, I have no plans. There are some pretty important milestones for the Center here, including new space, a

fundraising campaign, renewal of the Center that I feel I have a commitment to go through.

KD: And your energy?

MM: That's obviously an illusion and I'm sure it's wrong, but I don't feel that my energy is worse. On the other hand, can I cite as many papers and facts? Can I remember as many new generic drug names as I could in the past? Probably not.

KD: Is that a good thing? [chuckles]

MM: I don't know. I really don't know. It depends.

KD: That's true.

We've covered a lot of ground. Is there anything in thinking back on the forty or more years that we covered, actually, probably fifty, that you would do differently, any steps along the way?

MM: Well, I'm not sure I would think of it this way. I would think of it in the following way. Assuming that at any given note, if just a little accident made things happen a little differently, the trajectories would have been just *drastically* different. I don't think I look at those differences with any deal of horror or great longing. It would have been a different story.

KD: Sure.

MM: Those opportunities—I shouldn't say opportunities—those branch points happened. In many instances and at many times, the decisions were made just by accident, by osmosis, by Brownian motion. I don't think I sat down in any great [unclear] and said, "This is what I really want to do." They just happen. I think that's true in many, many people's lives.

KD: I would think.

[speaking to LK] Other things?

LK: I think they're covered.

KD: Is there something that we didn't ask that we should have, something that stands out?

MM: I really can't think of any… First, let me say that I never thought anybody would spend so many hours listening to my story.

[chuckles]

MM: This was a masterful interview, because you really stayed out…because these are things that you're intimately involved in. I really appreciate that. It was a wonderful interview.

KD: We thank you and the Academy. It's a gift to give time to reflect. Actually, it's a gift for everybody to get a chance to think back. We don't necessarily do that as often as we should.

MM: All right. Shall we have some lunch?

KD and LK: Yes.

[End of the Interview]

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