Dr. Mark Hallet Interview

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Dr. Mark Hallet Interview

Interviewer: Okay yeah, so maybe you can start recalling the time when you came to NIH. I think you came in 1984?

Dr. Mark Hallet: Okay, right, so I'll try to give a history of this is – do you want to talk only about MR or do you want to talk about neural imaging in general?

Interviewer: Yeah, in general, more general. See, I'm interested in both PET MR –

MH: MR and PET, okay. I actually had been a fellow here at NIH in 1970, from '70 to '72. But I was not involved with clinical things at that time, I was involved in basic science.

Interviewer: What did you do?

MH: I was doing membrane biophysics. After that I had my clinical training and I came back in 1984, just as you've noted. My interests have been always in the motor system, trying to understand the physiology of movement, and movement disorders and motor disorders. And one of the things that was appealing to me in coming to NIH was the use of neural imaging for further analysis of these problems. I had been largely involved in studies using clinical neurophysiological tools such as EEG and EMG. I had never done a lot of neuroimaging work. Of course, the field was relatively new, so I thought that would be a nice tool to add to some of the studies that we were doing.

So when I first arrived, the – it was prior to functional magnetic resonance imaging. There was only PET studies, and the studies that we had – the only ligand available for PET at that time was FDG for deoxyglucose, which looked at brain metabolism. We had no cyclotron at that time, and the FDG arrived by helicopter. I guess you probably have heard stories about that already?

Interviewer: No, not yet.

MH: Oh, you haven't heard that story?

Interviewer: No. [laughs]

MH: [laughs] Okay. So the FDG arrived by helicopter. I've forgotten where it was manufactured – manufactured somewhere north of here, I've forgotten exactly where. And it arrived by helicopter and then there was a car that would come to pick it up and it would bring it over to the NIH where we had our PET scanner. And the whole process of having it made outside of NIH and delivered by helicopter and the time delays meant that the FDG was often of not adequate quality for doing studies. So there were very frequently times when everything was prepared, including the patient and everything else, but the FDG was not adequate and the study had to be canceled. There were lots of cancellations in those days and people were very frustrated about the – about the ability to do work. Eventually, NIH did get some cyclotrons. Actually, I don't know exactly how this came about. We, of course, only I guess really needed one, but there was – we wound up buying two at the beginning. Exactly why that happened I don't know, but then they got installed and then the FDG was manufactured here on site and that made much more reliable of course.

Interviewer: When – do you remember when that was? And where was it installed?

MH: Well, it was installed underneath the area where the PET scans themselves were being done. And part of the reason for that was the next ligand that came along was radioactive water. And the radioactive water has an extremely short half–life, and in order to be able to do that it basically has to be manufactured right there and delivered almost instantaneously. And so it's manufactured and then squirted in and you have to have a great deal of proximity in order to get those studies to work right. So there was this shift from – in terms of doing functional studies which was the – my primary interest and the interest of lots of people trying to understand how the brain is functioning, to go to water studies from the FDG studies. The water studies had the capability of being able to do multiple studies in different states. Where the FDG is a very long study, so you really could only do one study or something like that with a patient, or maybe two on two different days. But the water allowed you to do multiple studies all on the same day and you could subtract them and see the differences so

there was a good deal of interest in moving to water from the FDG. And the radioactive water became the most popular, I think, ligand.

There was also some interest, early interest, in developing ligands for other purposes other than just plain functional work. I don't know the history of which ligands developed in which order. Peter Herscovitch, I'm sure you're going to be talking with – is that right? Do you know Peter?

Interviewer: I'm going to, yes. He's leaving, or he already left.

MH: Oh is that right?

Interviewer: Yeah.

MH: Oh, I didn't know that.

Interviewer: Yeah, so it's a little bit difficult to get a hold of him right now.

MH: Oh, I see. Well, Peter came relatively early on in this and was certainly there as all these different ligands were being developed, and he would I'm sure recall the order of all of these. But there was a good deal of difficulty in developing any ligand. It's always been very slow to develop new ligands. It is a tricky business to develop them and they certainly have taken a long time to develop. So — and again, what year all this happened I don't know exactly, but in terms of the functional studies which was our – which has always been our primary interest, at some point along the line it became clear that MR could be used for functional studies as well as PET, and that capability came into the MR facility. And then there was an interest in doing functional studies with MR rather than PET. Now, there was a transition that occurred over a number years in this regard for – because people had been doing a lot of the studies with radioactive water, but it became clear that the functional magnetic resonance imaging studies could be reasonably good. They had the advantage of higher resolution, and the fact that there was no radiation. So it was much better for a number of reasons to go with the functional MR.

Interviewer: So when you arrived did you start doing bed studies or did you –

MH: Yes.

Interviewer: Yes.

MH: Yes. Yes, we started doing FDG first and then we had this transition from FDG to water, and then we – and then the third transition from water to functional MR for the reasons that I was just describing. And actually, in the beginning, we had a few papers where did similar studies using water and fMRI to demonstrate that the studies produced relatively similar results so that one could do equivalent studies in the tube. So then, functional MR as it developed became extremely popular at NIH and the magnets were just added one after the other. [laughs] It was a very rapid growth in that field as people saw that it was useful for functional studies and the number of magnets increased dramatically. Now, there's always been a lot of people who were interested in working so that the time when the magnets has always been — at a premium even though we have lots of magnets we have lots of investigators so there's been lots of competition for time on the machine.

The techniques have evolved. The hardware has evolved. The analysis methods have evolved over the years. We began with scanners that were – I don't remember what the first scanners were. Maybe – I think they were less than a Tesla in strength. But then there was the 1.5 magnets and they were very popular for a long time and now the 3 Tesla magnets are almost completely taken over the 1.5 Tesla magnet and there's even a 7 Tesla magnet that's in development now but not really ready to use. So magnetic resonance imaging has a lot of different capabilities. The anatomical work, of course, has been where it first came in terms of doing very exquisite anatomical work. Then it began with the functional magnetic resonance imaging that I'm describing. And then other techniques have developed with magnetic resonance imaging as well which have – are now becoming more and more popular; things like magnetic resonance spectroscopy, diffusion MRI, diffusion tensor MRI. So lot's of techniques have been developed – have been developed for the use of the MR technology.

Meanwhile, back on the PET side, much but not all of the functional imaging moved from the radio water to the functional MR, as I've mentioned. And that has allowed more development on the ligand side for PET to look at the status of neurotransmitters and neurotransmitter receptors, for example, which I guess has been the most active situation with respect to the PET ligand work now. So people are looking at GABA receptors, looking at cholonergic markers or looking at different aspects of dopamine, both dopamine storage and dopamine transporters. That's been particularly active. So the work on PET has changed its emphasis. It still shows itself to be extremely valuable but in a different sort of mode from what it was originally in which the emphasis was on function or just sort of brain functions. Now it's been a little bit more on other aspects. So both PET and MR continue to be useful. And there still are some functional studies that we do with the PET because the MR is – even though it's good for the patient in terms of not having radioactivity, it is a difficult environment to work in. For example, it's difficult to make brainwave measurements at the same time as you're doing imaging in the MR environment. It's getting to be possible now, but it's been difficult. We wanted to do some studies with people sleeping and to record their EEG, and that was just easier in the PET than it was in the MR. So both of the modalities to be useful and they have evolved over time.

From the personnel point of view, the way things have happened, the PET has been largely controlled by the clinical center as a NIH wide resource and there have been a number of people who have headed up the PET facility over the years. Peter Herscovitch has I don't think ever been in charge of the whole thing. He had – he's been responsible for the clinical PET operation, but never for the whole operation itself as far as I recall, the organization. And all the institutes have participated in the PET activity under the general leadership of the – of a sort of central organization. There was some dissatisfaction with that in terms of an organizational scheme, and the MR has arisen in a somewhat different way in terms of how it's been organized. There has been the concept of the lead institute where it's a combination of institutes that have been interested in it, and one institute has taken the primarily responsibility of running the show with the help of the other institutes. So at the moment there's a lot of MR machines, some of them — the NINDS is the lead institute, some NIMH, some

NHLBI; I believe they're the three institutes that are the leaders for a number of the things – a number of the machines. But it is different from the model that was used for PET where the NIH as a whole was responsible for the management.

Interviewer: So when you came what section or unit did you start working in?

MH: Well, in terms of my own research I – when I came I developed my own research unit called the human motor control section, and I've maintained that unit over the years, it hasn't changed. It's grown in size but it's not been changed in any way. As you probably know, the main unit for doing research at NIH is the section. Sections are sometimes are amalgamated into branches, but it is the section, which is the main research unit. So that's my research unit that I developed and I have maintained it during the time that I've here.

Interviewer: Okay. And do you have – so the – this is your section, but do you – but the MR facilities that you have are located at the NINDS, or are they yours?

MH: Oh, I see what you mean, right. Okay, so the way that has operated, NINDS hired a facility manager to manage it both on a scientific and administrative level. So when we got the MR to run, we hired Alan Koretsky as our scientist, and he in turn hired Lalith Talagla to be a – the person actually managing the NINDS facility on a day to day level. NIMH hired Peter Bandettini to be the manager of their side of things. For a number of years – yeah, when I came in 1984 I was also the clinical director of the institute as well as being — running my section. I stepped down from that job in about 2000, and one of the responsibilities of the clinical director was to allocate time to the different research sections, which I did when I was clinical director, and now Henry McFarland is the clinical director so it's his job to do the allocation.

Interviewer: So do you remember if you allocated time what kind of studies were the most fascinating?

MH: Well, the most fascinating studies to me were of course to me [laughter] were trying to understand how the motor system works.

So I certainly found them the most fascinating. I think that the – there's been a lot of very exciting stuff that has gone on in all of these areas. It really depends upon your interest. I think that imaging has added a lot to almost everybody's research who has gotten involved in it. Take – well Henry McFarland himself, he's been very interested in multiple sclerosis, and his primary interest now is in imaging in terms of how it can follow lesions in multiple sclerosis and help understand the way that the disease is progressing. It's been extremely useful going back to the older stuff, the work in PET with even FDG was extremely valuable in understanding both brain tumors and epilepsy, and a lot of that work has gone into the clinic now. That's just the standard clinical practice. In the beginning, of course, it was research work that was developing, and that's moved into regular clinical practice now. If one has a brain tumor to help to find where it is and what its character is, to identify an epileptic focus, that's work that has really matured on the PET side into the clinic.

In terms of functional studies, people have learned not only how the motor systems works but almost every other system of the brain [laughs] in terms of different things. I guess one of our most exciting discoveries was one that happened by accident, and one that's gotten a lot of attention, is what is called "cross modal plasticity." We were doing some studies in blind patients looking at their motor system and discovered when they have somatosensory input it gets rooted to their visual cortex. So since they are blind they have no visual information going to the visual cortex, the visual cortex could just be empty, but instead what happens is the brain re–roots somatosensory information, that is touch information from the skin, to the visual cortex where it is processed in part. And we just came across that just by accident since we were studying the somatosensory motor system in the blind for other reasons which I won't go into. We just happened to find that information went over to the visual system. That was a big surprise to us. It turned into a nice publication in *Nature* and it has spurred a great deal of interest in terms of follow–up studies by lots of groups around the world in terms of how plastic the brain is and how this information can be re–rooted from one modality to another. That was probably one of the most exciting findings that we made.

Interviewer: So when you say you studied the – do you also study Parkinson's?

MH: Yes, yes, uh–huh, we have also studied Parkinson's Disease, that is one of the areas of our interest. We have – in fact, we've been carrying out a number of studies in Parkinson's Disease over the years, we have one that we just recently finished and just writing up using the MR technology, patients with Parkinson's Disease have difficulty making movements automatic. They have to think very carefully about every movement they make as opposed to a normal individual that after a while doing something over and over again you can do it automatically. For example, in driving a car you don't necessarily think about every turn that you make, you can do some things automatically. And even something as simple as walking, you don't have to think about each step that you make. But patients with Parkinson's Disease have to think about each individual movement so they have a difficulty in automating movements. So we've studied that using imaging and have found that what happens in normal individuals is that the brain begins to economize in a fashion that we don't completely understand where brain mechanisms – the brain doesn't need to work when everything has been automated. It just – the brain metabolism gradually decreases, but this doesn't happen in patients with Parkinson's Disease. When they work very hard they can get some simple things automated. But even when they automate a simple thing the brain metabolism remains relatively high so that they have lost this ability to have this brain economy that is necessary for automating things.

Interviewer: Do you have any idea why?

MH: Don't really know why that happens, although presumably it has something to do with I would guess with basal ganglia deficit that they have because of the dopaminergic deficiency, but that's not for sure.

Interviewer: So as a researcher, a scientist, how do you think? Do you think, "Oh, we have this technology available here let's do a study that we are now able to do with it?" Or are thinking more from the mechanical point of view and say, "I want to understand this and that problem and I need the technology to allow me to evolve technology?"

MH: Yeah, I think the best way to do research is to take a problem that you want to solve and then figure out the tools that are available to help you solve it. In some circumstances imaging can help and in some circumstance imaging can't help. I think it's probably a bad idea to approach a research and say, "Here we have a tool, let's find out some way to use it." I think it's much better to work from a problem that needs a solution, where you're sure that you're doing something that will have in fact some useful significance either from a basic science point of view or from a clinical point of view.

Interviewer: So how do you see — where is the research going at NIH in terms of imaging? Are they going to expand? Are they…?

MH: Well, the imaging at NIH has been expanding constantly so I suspect it will continue to do so. I think it's recognized as a very valuable tool for understanding human biology, and so I think it will continue to expand and the techniques will continue to evolve. MR in particular has been evolving very rapidly, every few months there's a different technique that is available and allows things that we can't do now. So we have problems that we can't solve at the moment, but if the MR tools become available for us then we might be able to – answer questions that we can't answer right now.

Interviewer: Yeah, and in terms of the evolution of thistechnology some of the research has been done at NIH so maybe you can point me to some of the other people who might be interested to talk to in terms of pushing forward?

MH: Yes, well in terms of our own institute I think Henry McFarland would be a good person to talk with since he has devoted his major research interest now is in imaging, and particularly with a multiple sclerosis slant. I think that Bill Theodore, or William Theodore, has been particularly interested in epilepsy. Steve Warach has been particularly interested in stroke. Now, he's come relatively recently but has been an innovator in both technology in imaging and the clinical applications of imaging to the stroke field. That was one of the reasons that he was actually brought here, because of his expertise in imaging and stroke. In other institutes,

Dan Weinberger has been interested in schizophrenia, has been a major user of the facility and has been a superb person. Leslie Ungerleider has been one of the primary users in NIMH in terms of its functional capabilities. She has a group that has a very heavy emphasis on neuroimaging. So there's some other people to talk with.

Interviewer: And in terms of – well so – well, the history, when did the machines arrive? How did they look like? Who might have photos of them? Who decided when NIH would spend money to buy them and so on?

MH: Well Herscovitch, if you could get a hold of him, would be the best person in PET since he – that's his balliwick. Another early person who was here when I came, Giovanni Dicuro [spelled phonetically], died, so he's not available, of course, anymore. You might be able to get a hold of some retired people. He had a physicist that worked with him, I'm blocking on his name now, but he actually built the NIH first PET scanner. He would be an interesting person to talk with. Although I haven't heard from him in years now and that's perhaps why I'm blocking on his name. [laughs] But the physicist that worked with Dicuro would be worth talking with in terms of the early history of PET in particular.

In terms of the early history of MR…one of McFarland's – oh, I'm having trouble with names today. One of McFarland's colleagues who works in the clinical center has been very much involved with this for a long time and is probably one of the people that would be able to tell you a lot of the history of the MR developments here.

Interviewer: Yeah, because at the office – the office, they want to document the research from [unintelligible] so they would like to get a hold of [unintelligible] documents, papers, anything.

MH: Yeah, yeah. Well some of the older – the old PET scans, I'm sure you could find pictures from this physicist who built it. I'm sure he photographed his own stuff, and whatnot. And yeah, I don't have any pictures of the machines, myself.

Interviewer: Yeah, well, okay.

MH: Okay?

Interviewer: Thank you very much.

MH: Okay.

Interviewer: Everything is fine.