

INTERVIEW

Reflections on three decades of clinical practice and clinical research



Joseph H Friedman* speaks to Adam Born, Assistant Commissioning Editor: Joseph H Friedman, MD, received a BA in Mathematics from the University of Chicago (IL, USA), then entered the Peace Corps, where he was a math teacher in Ghana from 1969 to 1971. He then obtained an MA in Mathematics from Washington University (MO, USA). He subsequently got his MD from Columbia University College of Physicians and Surgeons (NY, USA) and did his neurology training at the Neurological Institute of New York (NY, USA). He

has worked in Rhode Island since 1982, and is Professor of Neurology in the Alpert Medical School of Brown University (RI, USA), as well as director of the Movement Disorders Program of Butler Hospital (RI, USA). He is a member of the Parkinson Study Group and the Huntington's Study Group. He is active in the movement disorders field and has published over 200 peer-reviewed articles on Parkinson's disease and drug-induced movement disorders. His research focus has primarily been on behavior changes in Parkinson's disease.

Q Could you tell our readers a little about your career to date & how you came to your current role?

I finished my training and moved to Rhode Island in 1982. I had done a residency in neurology and spent a lot of time following around our very famous professor Stan Fahn, MD who's one of the major figures in movement disorders, and became very interested in that but I actually had not done a fellowship. However, when I moved to Rhode Island there were very few neurologists in the state and none of them were particularly interested in Parkinson's disease (PD) or movement disorders. I expressed an interest in this and gave as many talks as I could to make sure people knew that I was interested and I attracted an increasing number of patients with movement disorders.

In 1985, when the Parkinson's Study Group was first beginning, I read an article

in *Science* talking about the establishment of this group that had the goal of creating a consortium of clinical researchers who would focus on clinical research related to PD. They were particularly interested in exploring medications that might slow down disease progression. I contacted the people whose names were listed and told them that if they were expanding beyond the original few centers, that I was interested. When they started writing up their initial NIH grant proposal they recognized they needed around 20 centers and so I was invited to participate. By attending these meetings I was able to meet probably all of the established North American investigators in PD, who were generally the same ones who did work in movement disorders in general. That was a very important foundation stone for me because it allowed me to develop a research organization at

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my hospital. It was small with just really one research coordinator. The study group got a grant in 1986 from the NIH to look at selegiline as a drug to slow down disease progression and so I had a coordinator who could help me run studies, and by being in the Parkinson's study group I was able to network into other drug studies for Parkinson's and I have continued my research activities into PD since then.

About the same time I had the opportunity of working part-time at our one state psychiatric hospital in Rhode Island. Because of my interest in movement disorders, I was very interested in tardive dyskinesia, which is a movement disorder induced by antipsychotic drugs. The psychiatric hospital didn't have any neurology consultants but they did have state money available for a part-time person. They didn't have that many patients, about 330 patients when I started, but this was an opportunity for me to be given hard money and do clinical research projects at the same time. I took advantage of the opportunity. That actually was another extremely important piece that fell into place in the long run for my research interests because while I was working there part-time, and I was interested primarily in tardive dyskinesia and other drug-induced movement disorders, the hospital was involved in the clozapine trial for refractory psychosis that led to clozapine being approved in the USA and, ultimately, released in 1991.

Now, clozapine had been under investigation in the USA for treating schizophrenia in the 1970s. However, when it was released in Europe it led to the recognition that it caused agranulocytosis in a small percentage of patients and a number of people died in Scandinavia. When that happened the drug was withdrawn in Europe, but was ultimately released when they recognized what the problem was and developed a monitoring scheme so that they could avoid any kind of similar problem, but in the USA it was not allowed back – even for testing – until the mid-1980s.

While I was working part-time at the psychiatric hospital, the other half of my time I spent at a general hospital seeing out-patients. One of the difficulties in treating

PD patients at that time was psychosis, because the medications that we used, and continue to use, for treating the motor aspects of PD lead to hallucinations – visual hallucinations – in about 30% of cases, and about 5–10% of all patients treated with these medications develop paranoid delusions. At that time the only way to treat them was to take them off their Parkinson's medicines, in which case they became very stiff. If you put them on a first generation antipsychotic, the patients also became unable to move. Clozapine, at that time, was billed as an antipsychotic that didn't cause any movement problems. It didn't cause parkinsonism, so it seemed obvious to me that you might be able to take a PD patient who's having psychotic symptoms from the drugs that they needed in order to move and maybe treat their psychotic symptoms with the clozapine. So I applied to the company and then to the US FDA to get a license, to use clozapine in a compassionate-use protocol. I became the only neurologist in the USA that had access to clozapine before it was commercially released and what I discovered was that it was a wonder drug for treating psychosis in PD.

That led to my interest in treating psychosis in PD and, as a result, I was the first person in the USA to embark on a treatment scheme. Even though the drug had been available in Europe for years, there was only one paper involving four patients where they used clozapine for treating psychosis, the authors concluded that it was helpful and then they dropped the topic. However, I started using it and pursued the topic, ultimately ending up in a double-blind placebo-controlled trial that was sponsored by the FDA and published in the *New England Journal of Medicine*, which led to an increased interest among doctors treating PD in looking for treatments for psychosis and in our current treatment regimen. Every antipsychotic that followed clozapine was tried in PD. I have written papers describing my experience with most of them.

So a number of unusual things fell into place for me, but clozapine still has to be monitored for its blood count problems as

1–2% of people develop agranulocytosis. It was a difficult drug to use. Especially for PD in New England, people had to go to their blood drawing station once a week, they had to go to their pharmacy once a week, my secretary had to get the blood count and then call the pharmacy and it was a real hassle. Then another drug came out, the atypical risperidone, which seemed like it would be the solution – we could use that drug. And so I used risperidone but unfortunately it causes a lot of motor side-effects and wasn't tolerated, but that led to a publication and then the next drug came out, which was olanzopine, and then drug after drug after drug and it sort of led to a research focus on treating psychosis. It also made me much more aware of the behavioral problems in PD. At the time I was interested in this, these really weren't recognized as being significant issues, everybody that treated PD really thought about tremor, rigidity, slowness, walking problems, speech problems, all the motor problems they had, and sometimes they would also talk about depression because depression was common in PD, but the other problems in Parkinson's like anxiety, apathy, dementia and fatigue weren't recognized as being significant problems. So I published one of the first papers, it was actually 3 months after the first publication but they were probably both accepted about the same time, one of the first publications recognizing fatigue as a major problem in PD.

After that, articles came out about fatigue and by around 10 years ago when people started looking at quality of life issues around PD it became well recognized that the behavioral aspects of Parkinson's are generally more important determinants of quality of life than the motor aspects, and the psychiatric complications that arise in PD are generally the single most important precipitants for nursing home placements in PD, not the motor dysfunctions. So I got in early on this recognition of behavioral, and then also other non-motor but not behavioral (like sympathetic dysfunction), problems in PD so that these days Parkinson's is well recognized as a neurobehavioral disorder, not just purely a movement disorder, even

though the doctors who primarily care for it are people like myself who are movement disorder specialists.

Q What is your research focusing on at present?

My particular research focus is still on the behavioral aspects of PD. In addition to participating in multicenter trials where other people are the lead investigators, we've also been interested in both prospective and retrospective studies. So right now we're looking at summarizing our experience with electroconvulsive therapy for the treatment of people with Parkinson's, problems that have generally been either depression or anxiety with PD. We are about to complete a study looking at rasagilene (or azilect), which was the subject of a study trying to demonstrate that it slowed the progression of the motor symptoms of PD. We're looking at it to see whether it might slow progression of behavioral problems or neuropsychological problems in nondemented PD patients. That study is almost complete so I don't know the answers yet. We're about to look at a study of apathy and fatigue to see if there's a relationship between the two, both being syndromes of decreased motivation in people with PD, and we're going to compare our results to the same study being done in patients with multiple sclerosis (MS), where fatigue is a very big problem, to see whether there's a relationship between motivation and fatigue and also whether the kind of fatigue people with Parkinson's have is similar or different than MS and whether there's a similar relationship, if we find any, with amotivation in MS, as may be the case in PD.

Another study is looking at a symptom that Lisa Shulman reported as very common in PD in the 1990s, which was something she called internal tremor. Many people with PD have a symptom where they feel like they're shaking or trembling even when they're not. They may feel this in their limbs, and it feels to them like the same tremor they get when their Parkinson's causes tremor, but when they look the limb is not shaking. They often also feel the tremor internally. They may describe

feeling a tremor in their chest or abdomen, which cannot really develop a tremor, or they may feel like their inner organs are vibrating. We're looking at that and also comparing that with MS where I've been told it's a common symptom. So again, research looking at things that have more to do with behavior and symptoms rather than motor dysfunction.

Q You have several research areas – how important do you think an interdisciplinary approach is to the understanding of movement disorders or neurological disorders in general?

I think an interdisciplinary approach is very important, I've actually attempted, but have had difficulty, in getting a psychiatrist to work part-time in my clinic. I take care of all aspects of the disease of course, I take care of the behavior as well as the motor dysfunction that people with Parkinson's have, but it's very helpful to talk over the behavioral problems with psychiatrists. They have a partly different outlook, because they perhaps see anxiety or depression from a background in which they've dealt with anxiety and depression in people who don't have PD, so that they're much more attuned to any kind of differences there might be between Parkinson's anxiety, whether that's a specific entity, or Parkinson's depression, whether that's different from the depression they ordinarily run into. Plus they often have, or usually have, a greater experience with the various drugs that we use because they use them on almost every patient that they see.

I have worked with neuropsychologists and sometimes exercise physiologists. I've been part of studies or tried to do studies on exercise for fatigue or looking for physiological differences between people with fatigue and people without fatigue who all have Parkinson's, so I have collaborated with exercise physiologists. For people with PD generally their problems are often interdisciplinary. It can be very difficult for the neurologist alone to try to understand them because sometimes other things are involved. There are Parkinson's patients, for example, who have problems with shortness of breath and don't have any cardiac or pulmonary explanation

that can be found, which I think is related to their Parkinson's, though it's possible it could also be anxiety, which can do the same sort of thing, and trying to get pulmonary physiologists to look at this would be very helpful. Overall I think interdisciplinary studies are very important and most studies should probably be carried out with as much interdisciplinary communication as possible.

Q How important is the doctor–doctor relationship in your field?

Well the doctor–doctor relationship is very important; I think there are different kinds of relationships among doctors. There are the relationships where we act as the specialty consultant on a case so that a general neurologist or internist turns to us for our expertise and they want to hear from us, and then there's the expertise that we get from our colleagues. I like to think I know a lot about PD and that I know a lot about behavior problems, but I also recognize that there are people who know more about some of these problems than I do, and certainly there are people who know more about other movement disorders than I do, and it's very helpful for me to have some people who I consult in cases where I'm unsure what's going on. So there are some psychiatrists who I will turn to for help, there are neurologists in movement disorders who I may turn to for help and sometimes other movement disorder specialists will ask me for my opinions. So there are those kinds of consultations that take place and then, of course, I publish. I publish a fair amount and that obviously is to spread my knowledge and what I may have discovered to other neurologists in general, but also any doctor or anyone that reads the manuscripts, to help them treat patients better. So I think that the relationship we have with our peers is very important. I like to think that I'm approachable and people might want to ask my opinions about certain things and I'm sure that's true for all my colleagues as well.

Q Is there any difference in the patient–doctor relationship in neurodegenerative disorders?

The patient–doctor relationship is an interesting concept because I think it's different

in different patients and it's often difficult to understand what the relationship is. I have a general approach to treating my patients where I tell them that I'm their consultant, they don't need to do what I recommend and that I view my role as similar to that of a financial consultant. They may go to a financial consultant who suggests they buy certain stock or they sell certain things and they take their advice or they don't. I never say to my patients if you don't want to do this, don't come back. I will always say: "This is what I think is the best thing for you, if you don't want to do it that is your business but I'll see you again in 3 or 4 months". I try to instill in them the idea that we are all working together, that it is a team approach, them, me, their families and whoever else is involved in their care and we want to do what is best for them. Some patients like to be told what to do, the old patient–doctor relationship where the doctor knows best. Some patients like the idea that I espouse being a consultant and when they come back and I ask "how did this drug work?" and they say "well, I never filled the prescription", I say "that's your business". But they can feel relatively comfortable about telling me that.

It is really quite different from one person to the other. I have now been in practice in Rhode Island for 30 years and I act as the primary care doctor for my patient's movement disorder so I get lots of telephone calls from my patients because if they have a problem related to Parkinson's – and many of them think that all of their problems are related to Parkinson's – they'll call me first, not their internist. So I interact with my patients quite a bit, and what I have come to think over many years is that the most important role that I fill is just being available. That after a time, there's often very little we can do for these patients. When somebody has Parkinson's, having had it for 20 years, having had every medication we have and they come back there's really not much we have to offer them. But just being available, just being able to listen to them, commiserate with them, to answer their questions, that alone in the long run is probably the most important thing we do for them

beyond what any medication adjustment accomplishes.

The patient–doctor relationship is really very crucial, especially long term, and since we don't have a cure for PD, I tell my patients that I'll be happy to be their doctor until one of us dies.

Q What would you say has been your greatest academic achievement to date?

I really think it was the clozapine study that was published in the *New England Journal of Medicine*. Showing that low-dose clozapine improved psychosis in PD, that it helped tremor and that it was well tolerated. I think, in my own mind at least, that was actually a major contribution to the treatment of PD because it accomplished two things. One, it underscored the importance of psychosis in PD and number two, it showed that it was treatable. It also led to neurologists being willing, not all of them but especially the Parkinson's neurologists, to start seeing these psychiatric problems as being something they should take care of. There were six centers involved in that study, one of them was a geriatric psychiatrist, the rest of them were neurologists who specialized in PD. This showed that this was a complication largely related to the medications that we were giving and we should treat it and we can treat it. I think, and again it may be a self-inflated image, but I think it was a very important study for PD treatment in general. I'm very proud that it was, not so much my intelligence or my creativity because it really wasn't that at all, but my diligence and my willingness to stick to this. It had been a study I had been trying to do for 10 years until somebody gave me the idea of where I might be able to get funding for it and then I got the funding, did the study and it was obviously a big success.

Q What do you enjoy most about your educational commitments at Brown?

Well I teach primarily residents, I used to have fellows but we've lost funding. So I teach neurology residents, they have an outpatient rotation in movement disorders so they spend some time with me. I teach geriatric psychiatry fellows who have a

requirement of rotating with me. I teach geriatric internal medicine fellows who also have to spend time with me and a majority of the psychiatry residents, because I work at Butler Hospital, take an elective to learn about movement disorders with me. I spend a lot of time teaching, not so much to Brown medical students – I do that to a very limited extent, I enjoy that but it's mainly teaching residents.

It's unusual because it's a neurology rotation but a lot of my patients do have psychiatric problems and my students always find it interesting to be exposed to the psychiatric problems because most psychiatrists don't see Parkinson's patients with these problems, or if they do they might see one or two a year and not really get the understanding, whereas my doctors who spend time with me will see 15 in a day and half of them will have some sort of psychiatric problem. So within a few days they get a very good flavor of the kind of problems we encounter. Generally they enjoy it quite a bit; they learn some neurology and some geriatric psychiatry.

Q Which is more important, education or research?

I think they're both equally important, I can't say that I like one or the other better or one is more important than the other. I think that if you make an important research contribution, which say the clozapine was – I think that was really important for patient care and I believe that improved the lives of many thousands of people with PD. On the other hand, I have trained some residents, hopefully they have improved their skills so they're better at treating this sort of problem. I've also trained a few fellows, some of whom have really done outstanding things in PD and other movement disorders.

Seeing patients participate in education, particularly of residents and fellows, as well as research – all three aspects are very important to me and each one provides a different sort of reward and if I had to give up one or more than one it would really diminish the enjoyment I get out of doing my work. Overall I would say that they're all about equally important and provide different types of rewards.

Q What are you excited about working on over the next year?

I'm really particularly interested in the study we're about to start with a student looking at apathy and fatigue in Parkinson's and MS and also exploring this issue of internal tremor. I have the feeling, just based on my own clinical experience, that this internal tremor business is actually fairly common and nobody knows about because there's only a single paper published almost 20 years ago about it. I really think that if I'm correct in this that it's going to be something along the lines of restless leg syndrome. Restless leg was something nobody noticed until about 15 years ago and now all of a sudden it's this major, uncomfortable syndrome that many people have and they have drugs for it that get advertised on television. I think internal tremor may be something along that line. I'm very excited to find out what we're going to learn about that and I'm very interested in this issue of fatigue, because it's such a big issue in PD and if we can learn something about it that might lead to better treatment. Although it may not be the most exciting and sexy area of study, nevertheless it would lead to a lot of patient improvement and a lot better quality of life for Parkinson's patients. Fatigue is such a big problem in this area and something very few people pay attention to.

Q Finally, what do you think will be the hot topics in the field of movement disorders over the next few years?

While internal tremor might be, it may turn out that I'm completely wrong and it's not such an important thing, it's not all that common. But I don't know that, so that's possible. I think the most important issues or topics in movement disorders in general is trying to stop disease progression, at least that's true for the degenerative diseases. PD and the related disorders like progressive supranuclear palsy, cortical basal degeneration, all of these sorts of disorders, especially Huntington's disease. I am hopeful that at some point there will be a dramatic breakthrough in Huntington's disease and the other similar inherited disorders, at least the polyglutamine

repeat disorders, maybe some of the other genetic disorders where researchers will be able to use some sort genetic engineering, as with RNA interference or something along that line. Perhaps being able to knock in some normal protein or detoxify an abnormal protein in these illnesses and that we may be able to treat or prevent the onset of diseases like Huntington's disease and the spinocerebellar ataxias.

Q Are you optimistic for the future?

I'm very optimistic about the genetic disorders. I'm less optimistic in the short-run for the other degenerative disorders like PD where we don't really know what the cause is. I think the biggest problem is pretty clear, that there are multiple causes and there are multiple forms of PD and although they may all end up with a final common pathway there may be lots of different pathways that get you there. Thus, it may be extremely difficult trying to figure out a cause because people may be looking at a collection of several different disorders and trying to identify one cause when the different disorders are in fact different.

They may be all heterogeneous with different etiology which might make it just impossible because researchers are looking at five samples and they've got five different diseases which they're all calling PD. It is a very challenging problem and that's obviously the same problem research is running into in Alzheimer's disease.

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