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Dr. Peter Basser

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Claudia Wassmann: This is Claudia Wassmann and today's date is Wednesday March 2, 2005. I'm conducting an interview with Dr. Peter Basser.

[break in audio]

CW: [laugh] You don't have a problem with this, but I do. So you had just started telling me everything I wanted to know –

Peter Basser: Okay.

CW: -- so I'm hoping you will repeat it.

PB: Okay, okay. Well you asked me when I came here and it was – I had formally came in 1986 but I didn't start working here until 1987, and it was in the biomedical engineering – called the Biomedical Engineering and Instrumentation Program at that time, and I was hired in the mechanical engineering section and my background had been in fluid mechanics and medical equipment development graduate school and I expected to do similar kinds of activities here at the NIH, but as I had mentioned before, the opportunities to do that were becoming more and more limited because physiology and cell biology were at that time in the decline, and molecular biology was becoming the dominant activity here on campus. And so increasingly there were fewer and fewer opportunities with people with engineering backgrounds to find a meaningful set of research activities to be involved in on campus.

But I did find some interesting applications in two areas. One was in drug delivery and transport of drugs which was still considered to be a very important area and worked with some of the mechanical engineers here, Bob Dedrick, Paul Morrison and I worked with Mark Hallet [spelled phonetically] and Brad Roth in the area of magnetic stimulation. The reason that I think that's important in terms of the invention and development of DTMRI is that those two project actually provided the impetus for the development of DTI, so it's not inappropriate to discuss them in this context.

In the case of drug delivery, the first one, Bob Dedrick and Paul Morrison and others in the chemical engineering program here had been working with Ed Oldfield and they had proposed a very novel drug delivery strategy which is now called Convection Enhanced Delivery or CED and they, Bob and Paul, had conceived of infusing drugs into the brain, into the extra cellular space to overcome the blood brain barrier, particularly for people who suffered from cancer, various brain tumors, where the blood brain barrier prevented drugs in the body from getting to the actual cancerous tissue in the brain. And this direct infusion was a real break through, but there was some attendant problems with it. That is when you infused into white matter or near white matter in the brain, they found in some of the early experiments in cat brain that the drugs would shoot along what we later identified were white matter tracks and that's how I actually got involved in the project because I had a background in porous media theory and I was starting to help them with the idea – you know the mechanical processes of drug infusion, because the hydraulic permeability or resistance of the white matter was so different along the fiber tracks as apposed to perpendicular to them, and because it was so different to the surrounding gray matter the drugs didn't go where they expected them to, they shot along the white matter pathways and at that time were really unpredictable paths.

And I realized at that point that we needed to know what the hydraulic permeability map was. Not just how it changed from tissue to tissue, from region of the brain to region of the brain, because it was heterogeneous, but it was also anisotropic -- there were preferred directions along which the fluid would flow and we had actually the same issue in magnetic stimulation. You know Brad and I had developed a model of how electric fields interact with brain tissue and we had parenthetically in one of our early papers talked about how electric fields would affect a nerve that was curved or kinked and we – and I came up with a little model to describe how magnetic stimulation would work if the nerve weren't straight anymore, but took a sinuous path, which all of them do in white matter. And without knowing the pathways of the nerve I also knew that we would be unable to ever find out what the effects of magnetic stimulation of the brain would be. So I was really primed at that point to find out a way to look at the anisotropic and heterogeneous electrical, mechanical properties of brain tissue.

Actually the first exposure I had to diffusion imaging was a talk that Denis Le Bihan had given. He had recently come to the NIH from France and talked about how diffusion could be used – I think it was in stroke and I thought it was very interesting, but I didn't really initially make a connection to it, but in the early '90s. Denis Le Bihan and, I believe it was, Phillip DeWeck [spelled phonetically] had a poster presentation at one of the NIH research festivals off in a corner there and one of the white tents that they had constructed over here in the parking lot. They had done something very novel. They had shown that they could color code different parts of the brain according to what they thought was the orientation of diffusion, and that was a poster that resulted in a paper I think early in the next year by Denis and Phillip. But I visited that poster and I was there with my friend and colleague Brad Roth, the guy I was doing the magnetic stimulation with, and I realized that there was something really fundamentally wrong with the approach that they were using because they had -- they knew, as I found out others did in the field at the same time, like Mike Mosely and others, that water diffusion in the brain was anisotropic and they used a – I don't know if this means anything to you, but they used a scaler model of water diffusion. They used a model that assumes essentially that water diffuses at the same rate in all directions. And I knew that it had to be described by a tensor [?] at least, just the way the hydraulic conductivity has to be described by a tensor or the electrical conductivity in the brain has to be described by a tensor, and I started asking Denis Le Bihan all kinds of questions without really tipping my hand and I said, "Well how do you measure diffusion in different directions?" And, you know, "What do you – aren't there other components that you have to consider," and you know things like that, and the thoughts were kind of racing through my head at that point about describing this with a tensor because I realized since I had a background in applied mechanics that once you have a tensor description of a material you have a tremendous amount of information about it that you don't have.

But I wasn't really – I was kind of coy about it frankly. I didn't want to sort of tell him what I was thinking which is maybe a little disingenuous, but I think scientist are unfortunately have to be a little protective these days, and I raced back to the lab and I was almost manically describing to Brad Roth on the way back this sort of picture of diffusion tensor imaging that was – that I was imaging where you would actually measure not a scalar diffusion coefficient but a tensor. And actually, very busily for the next few days, I was writing up a prospectus that I wanted to share with Denis and his colleague Robert Turner whom I knew and was friends with, and I came up with the idea of fiber track following, the eigen values and eigen vectors of the diffusion tensor providing useful quantities that people could image with. The invariants of the tensor like the trace and other things that determine it, that could provide useful information about the fiber orientation and tissue properties and I showed it to Denis.

I brought with me this multi-page disclosure, if you will, and he said he was very excited about it, because he knew that this was something that wasn't being done and had real potential but he said in his thick French accent he said, "There's one problem." He said, "You know we don't know how to measure the tensor." So I left the meeting very discouraged because I had this idea but we didn't know how to measure the quantity that I wanted to measure and specifically they didn't know how to measure the so called off diagonal elements of the tensor. So Bob Turner and Denis had suggested that I go back and read some of the classic text in the diffusion imaging area, like Carr and Purcell [spelled phonetically] and particularly the work of Stejskal and Tanner, which I was totally unfamiliar with and I spent days pouring over those articles, particularly Stejskal and Tanner's articles, and I realized there were a couple of formulas that were very relevant to what we were interested in and I studied one formula in particular in which actually Stejskal and Tanner have a tensor, a diffusion tensor, in their equation, but nobody had actually measured that quantity. It was kind of a theoretical interest and I realized that that expression was – turned out – just a mathematical point but the signal intensity that was measured in the NMR experiment was related to the scalar quantity, which was essentially a projection, a quadratic form, and it wasn't obvious from the way Stejskal and Tanner wrote it that it was this mathematical type that it was called a quadratic form. And when I re-wrote it in the way that I was familiar in the vector notation I realized what it really was it was a simple relationship between the single that you measured and the projection of the diffusion tensor that appears in the block equation along different directions.

And then the question was could you measure or estimate all the components of the tensor from that equation, and I realized that if you applied gradients in more than three directions, it turns out six directions, that you can get enough information, you could get enough samples of the orientational distribution to be able to invert that equation and to be able to solve for all of the elements of the tensor and I kind of excitedly wrote Denis Le Bihan an email at that point and asked him – I didn't even know whether you could apply gradients in different directions other than X, Y and Z because I had so little understanding of the gradient hardware and he said, "Yes" and I said, "Well in that case then we can measure all of the elements of the tensor."

That was a very exciting moment. I don't know if you're – if you're not a scientist and you're not interested in invention or discovery those kind of moments may kind of pass over as being not very significant, but those were the kind of rushes that you get in this business that really make it all worth while. You get this surge of excitement when you figure something out that you have a sense is more significant than the little problems that you solve on a day-to-day basis and it's really fun. I have to say that anybody who is willing to work for long periods of time and periodically get these moments of excitement I think – I don't know, for me it was just a very thrilling moment.

CW: And where did you take it from there?

PB: Well actually this was an amazing story too, because there's so many people involved and activities that had to be done in order to bring this from bench to bedside. So the first thing is Denis and I started corresponding, and Jim Mattiello then, who was working with Denis and who was also working in our program, was a little frustrated with some of the projects he was working on and decided that he wanted to start working with us. So I was excited about that because Jim had a technical background in MRI, he had been working in the area for a few – maybe a year and a half at that point, and he would provide a lot of experimental help which I really couldn't provide because my knowledge at that point of the NMRI hardware and sequences and things was almost nonexistent. And so we started doing diffusion experiments with water. The first thing that we – in pork loin – the first thing that we started doing was – Denis got us some magnetic time down at the NMRI center and we started to – since we had this mathematical framework that related the signal that we measured to the diffusion tensor the first thing that you want to do is show that the diffusion tensor in water is an isotropic tensor, which means that if you look at the diffusion process along any direction that it appears the same and that has a characteristic – a special form when you write it as a tensor and it's something that if you can't do that you can't look at other materials that are more complex. In fact –

CW: What year was that?

PB: Well 1991 was when I – it was around late September of 1991, I believe, when we had that science fair here at the NIH, and this would have been now in November/December timeframe in 1991.

CW: Okay and you started doing – measuring animals?

PB: No we – that was – those were a long time away. We started to look at water and glycerin. We looked at – I went to the Safeway and I bought pork loin ,and Jim who had came from an Italian background knew about something called spaghetti squash and he recommended that as something that we could look at. And we looked at -- basically we looked at water and pork loin initially and we wanted to see whether we could get the write tensor properties in water and whether we could see diffusion anisotropy in pork loin.

In fact people in the '70s, Hazel, Chang, Cleveland, others had looked at diffusions anisotropy in skeletal muscle – Hansen – and I had read some of their papers, but they didn't look at it they way we did. I mean the realized that there was diffusion anisotropy, but imaging created a special problem which was that -- you know tissues are heterogeneous and they may have different diffusion properties in different areas in different regions, and the fiber direction – the structure may be different in different places and since the materials are turbid anyway you can't tell by looking at it where those fibers are aligned. So, you know, this idea of being able to measure a local diffusion tensor and, you know, first without imaging gradients and then with imaging gradients was very powerful because it allowed you to take into account the fact that the tissue properties were changing from place to place.

The tissues that – the reason I say that is because when we wrote our first abstract describing it at the ISMRM I think which we presented in Berlin in 1992, we looked at a sample of pork loin and we showed that we first measured the diffusion tensor for a large region of that pork loin specimen, and then we actually physically rotated that – Jim Mattiello [spelled phonetically] actually physically rotated the pork loin specimen in the magnet. We repeated the experiments, calculated the tensor and we were able to show that the directions that we calculated for the pork loin muscles followed the direction of the rotation that he had applied physically on that sample, so that we were measuring something intrinsic to the tissue. These principle directions that we were able to extract from the diffusion tensor were fundamental to the tissue architecture and were independent of the coordinate system that we made the measurement in, which was really, I think, a very important demonstration then.

So we actually played around with the pork loin and the water for a long time because as it turned we weren't able initially to get the water diffusion properties to look isotropic and we, for a long time, were trying to figure out what it was, what artifact we were seeing. And it turns out that because the diffusion measurement is so sensitive to small variations in the gradient strength, you know, in the scale even of the gradients, the eddy currents and other perturbations that we were having trouble making water look isotropic. Actually that led to another part of, I think, our original patent disclosure which was the idea of using the diffusion tensor to calibrate gradients.

You know Denis had pointed out that the diffusion sentization, that the attenuation of the diffusion signal went with the square of the gradient and the signal that you measured using phase changes goes with gradient itself. So it turns out that the diffusion signal is much more sensitive to the gradient value than the phase image and could be used as a way of calibrating the gradients and, you know, it occurred to me that maybe one of the things that we should do is if we can't – we know that water is isotropic and we're not getting an isotropic tensor, why don't we use that to recalibrate the gradients to essentially correct them in software, because we know what the value should be and we know what we're measuring so there's obviously a systematic error and we could use that to correct the gradients in a tensorial way. So I had worked out the theory for that and then we eventually put that into our patent application.

Now going from bench to bedside which was a whole exciting story in itself, because after Denis and Jim and I -- and we worked very well together we all brought different things to the table clearly -- after we had worked on the project for maybe a year and a half both Jim and Denis announced to me within a very short time that they were leaving the NIH. Denis got an offer that he couldn't refuse in France to be apart of the Atomic Energy Commission and run a very large program, and Jim Mattiello decided that he wanted to go off and be an entrepreneur and run a robotics company in Michigan. And I was devastated because we were really making such fantastic progress and this team was going to be broken up and we would never -- I thought that this was – could basically grind everything to a halt.

Luckily people in the field, with the exception of maybe one or two groups, totally overlooked our work and seemed to show no interest in it at all. In fact one of our possibly greatest potential rivals, a graduate student who was working at Mass General at the time, apparently was told by his thesis advisor to avoid doing work in this area because it wasn't going to go anywhere. So we had a little bit of breathing room as it turned out, and Jim left and Denis left and for about six months I was at wit's end because we needed to acquire data and we needed to move the program ahead and work with animals. It turned that just around the time Jim left I started to spend time with an Italian post-doc named Carlo Pierpaoli. Carlo at that time had just recently come from Georgetown University, I believe, where he was working on benzodiazepines and other drugs that affect cognitive performance, but he was very interested in MRI and in diffusion and was familiar with Denis Le Bihan's work and was hearing about what we were doing with Jim Mattiello. And he approached me, if I recall about the possibility of working together and I was a little leery because I didn't know much about him initially and, you know, I didn't know what the collaboration could lead to, but the more time I spent with him I realized he was a brilliant very serious person who was learning the diffusion technology very quickly and was genuinely interested in DTI, and as time progressed we started to work very closely together. He got the software from Jim Mattiello and he started to adapt it and he was interested in clinical problems.

His background was in neurology, which was – turned out to be exceptionally helpful and he turned DTI really into his major research focus. At that time also he was working with Alan Barnett in NINDS and Alan was a physicist, and he and Alan started to work very closely together to develop MRI sequences that would allow you to do these experiments in animals and eventually humans and working with Alan and then eventually with Peter Jezzard, Carlo really created an infrastructure to do human MRIs at a very high quality. Denis and Jim and I had actually attempted to do this in 1995, and we have an article in Denis's book and we have a figure that shows I think it was my brain, it shows corpus callosum, but it wasn't a full three dimensional DTI acquisition, it was a diffusion ellipse image rather than a diffusion ellipsoid image, but it shows the sort of arcade shape of the corpus callosum very clearly, but artifacts on the [unintelligible] scanner and the eddy current artifacts and the stability, the homogeneity of the magnetic field was poor, and so we really weren't doing high quality radiologically acceptable DTI. That was really just a demonstration that it could be done.

But Carlo and Alan and Peter Jezzard really developed a diffusion weighted imaging framework here that would allow us to do DTI voxel by voxel, with high enough spatial resolution, high enough image quality to be able to do this clinically. And actually Carlo got a very nice award from Storey Landis for essentially bringing DTI from bench to bedside effectively. So these sort of pork loin and cat brain experiment that we did, that Denis and Jim and I did, to being able to do this in monkeys, sedated monkeys, and then ultimately in humans. So I think a large part of the early bench to bedside migration was due to Carlo's coaching and effort and involvement in that project and the physics input from primarily Alan Barnett [spelled phonetically] and Peter Jezzard.

And then there was another period following the 1996 paper, clinical paper, where there was again a kind of flat – flat growth in the DTI field. People still didn't understand how to measure a tensor. They didn't understand it was, what information content it provided, except for a few groups, but I think that it was starting to be intriguing to enough groups that we realized that we had to make it a little bit more accessible. We -- unfortunately we wrote some early papers that made it seem more complicated than it is in a sense. We focused on some technical issues, specifically estimation of what is called the D-matrix. It was a very strong interest of Denis Le Bihan's and particularly Jim Mattiello because they had – Denis had played around with the cross terms in imaging -- in diffusion imaging prior to DTI and he thought that these were important and needed to be elucidated, and Jim was the one who calculated a lot of these effects so the papers we wrote about cross terms did put some people off in the field because they thought it was complicated and difficult to do.

So I realized that we had to – I don't know how to say it tact – well to dumb it down a little bit so that people wouldn't feel that it was so difficult to do, to make it simpler and more accessible to a larger group of people who otherwise wouldn't do it and we proposed – I went back to actually a special case of the paper that we had written in 1994 in which we would only use seven diffusion weighted images and I showed in that case you can get an analytical relationship between the measured signals from the MRI experiment and the diffusion tensor, and I published those formulas so that all you had to do was get your signals and plug them in and you didn't have to – it was you know a little black box and in the afternoon you could program it up and you didn't have to do any fancy statistical estimation or – you know nothing – no real computer programming. You could do this in an Excel spreadsheet if you wanted to. And in fact, shortly thereafter, GE picked this up and started to provide it to its sites as an add on in FuncTools [spelled phonetically] package and people I think for the first time realized that you didn't have to be a rocket scientist to do DTI. You could take your original diffusion weighted imaging data and you could process it with a slightly more complicated model, calculate the tensor and then calculate all of these useful parameters like the trace, and the fiber directions and make the maps of the fractional anisotropy and the other features that we had already presented and talked about and that it wasn't so scary. And actually a number of people have told me that before that paper came out that they were really not interested in doing DTI.

And then shortly thereafter there were – you know there was another increase in papers on the subject and people started…

[end of side A]

PB: Are you out of tape?

CW: Oh no [laugh]. No it's great to get the entire story in time [laugh].

PB: And then more and more I think there was enough of an interest I guess among the sites that General Electric decided ultimately to license the DTI technology from the NIH and some of the other companies followed suit thereafter, and after that point many clinical programs had the technology that they were able to use because it was provided either by physicists in their program or through these commercial sequences and analysis tools that the companies were starting to provide and there was a sudden surge in clinical applications, so you started to see papers applying DTI to many, many diseases and disorders. Frankly many of which I could never have anticipated when we first started. Particularly, what was particularly interesting frankly was the possibility of using DTI to look at some of the behavioral and cognitive disorders, psychiatric disorders, because I really – I viewed DTI primarily as an anatomical neurological diagnostic tool, initially, and then there were reports like from the Torkio, Cleansburg [spelled phonetically] Gabrielli study that suggested that there might be a relationship between the white matter organization and reading ability. I found that finding shocking, but it seems to have held up in some of Brian Mondell's [spelled phonetically] recent work; he suggests that as well. And there was a re-discovery at that point in the MRI field about what I guess we call the neural anatomical hypothesis which is that the brain wiring is – although people are all focused on gray matter and fMRI the white matter is important too.

CW: That was what I was going to ask.

PB: Yeah.

CW: What is the real advantage of DT-MRI over classical MRI is that you can picture white matter and classical MRI pictures only gray matter?

PB: Not exactly because there's – for instance T1 imaging provides – you know can provide a nice depiction of white matter where you can at least distinguish it fairly well and at high resolution from gray matter, but it doesn't provide the fiber orientation and it doesn't allow you to project tracks or calculate tracks. That's something actually I didn't mention in my telling, but maybe we'll get back to that how tractography came about, but the possibility of following white matter pathways is a very exciting information that DTI provides that the other imaging techniques don't. In fact Carlo Pierpaoli and Sinisa Pajevic again came up with a very compelling way of displaying the fiber tract information. We had proposed back in 1994 that the principle direction of the diffusion tensor, the one that's associated with the fastest diffusion coefficient, is the local estimate of the fiber orientation. Carlo and Sinisa realized that you could color code and I think just around the same time there Derrick Jones did too in fairness, that you could color code that vector with red, green and blue let's say and it would correspond to the X, Y and Z coordinates of the components of that vector and in doing that you could make a map of the brain where you could see the direction of the fiber by looking at the color.

Denis had actually proposed a color scheme back in that poster that I talked to you about, but it was very, very different in the information content. This was really a way of taking the – Carlo and Sinisa's approach was to take this fiber orientation that we calculated from the diffusion tensor itself and to assign a color to it that was related to its orientation in space, and it's turned out to be a very, very powerful way of, by eye, looking at white matter pathways, primarily the large white matter pathways, the motor tracts and the sensory tracts and the association fibers, the commissural fibers, projection fibers. And in fact Carlo and Sinisa wrote a very beautiful paper where they showed that for the first time you could with DTI you could really visualize those pathways and their orientation and tractography in a since mathematically connects the dots. It allows you to compute those trajectories that your eye is telling you exist in those color maps that Carlo and Sinisa had produced.

In fact the tractography dates back to – at my 1994 disclosure I mean I showed actually Denis pictures of these fiber tracts as though I could calculate them. I rendered them in mathematic and showed what a fiber field might look like. In fact if you want I could pull that down and show you my notebook, but the realization of that took a while because the data was so poor initially. The idea of doing tractography on this noisy sparse DTI data set seemed like science fiction to me back in 1994, but already towards the end of the '90s tractography started to become a reality because the quality of the diffusion images were so much better and the resolution was finer and the possibility of doing tractography was much more palpable. It was a next step, but the –

CW: So was that a matter of development of MRI machines?

PB: No in fact it was post processing. Once you –

CW: [unintelligible]

PB: Yeah once you have the tensor field, once you have the tensor sample then each voxel within an imaging volume you can construct these fiber orientations in each voxel and then – you know my background is in fluid mechanics. So you have to realize I learned about streamlines and streamed surfaces as a graduate student. So the idea of following these lines of maximum diffusion was really very similar to what I would have done in graduate school if I wanted to follow a flow field in a laminar flow. If I wanted to let's say show were a fluid was flowing in a curved pipe I would have used the same kind of equations that we proposed for following the direction of the maximum diffusivity. There was a little bit of a trick which was that you had to – the way that I had conceived of it you had to have a model of a diffusion tensor field, a continuous model, and that held up DTI / tractography probably for 4 or 5 years for me, because [laugh] that's another story.

Akram Aldroub who was here working and who had developed some of the mathematical machinery to do this tensor field approximation was very excited about doing this work but he was so brilliant that he had so many other things that he was working on that he never got around to doing the tensor field approximation. I kept bugging him about it and bugging him about it, but eventually he decided that it was important enough that he had to do it and he and Sinisa Pajevic -- Akram's theory and Sinisa's implementation provided the software to be able to essentially weave together these discrete measurements that we make in individual voxels and turn it into like a fabric that you could follow seamlessly through the brain and once that fabric was created then it was a simple model to solve a differential equation along one of these fiber tracks, but it's just a mathematical model. A lot of people don't realize it. We just take the diffusion data and we just follow along on the direction of maximal diffusivity. Those fibers are mathematical objects that are extracted from the tensor data. They're not actually measured independent – independently. So –

CW: So where do – where do you see it going? Do you conceive of it more as a diagnostic tool or are you still interested in drug delivery?

PB: Well you know we're going back to magnetic stimulation and drug delivery again, which is interesting. It's back to the future. I have a collaboration with Melissa Santornarit [spelled phonetically] who is at the University of Florida and she wants to use DTI for personalized drug delivery, particularly in some intractable tumors like in the ponte fiber area. Where it's very hard to operate and where this chemical drug delivery can provide, potentially provide real relief; and with Pedro Miranda [spelled phonetically] we're going back now to looking at magnetic stimulation using the electrical conductivity properties, the heterogeneous and anisotropic properties that we're able to extract from the tensor data, and now we use [unintelligible] element approaches and we're using the tensor data to make a better model of the electrical properties of the brain. So in fact those initial problems that got me interested in them in the first place we're now in a position to revisit with a lot more information. Now the convection enhanced delivery – really a therapeutic application. And Carlo Pierpaoli is working with neurosurgeons here at NINDS to help with surgical planning, to do DTI to see where the nerves are and what the – to look at tumor staging and to find out what's healthy tissue and what's edema. So again it's been used in a therapeutic application, which is a little bit surprising from the history of the ideas, but I think primarily it's still a diagnostic tool.

I still view it primarily as a diagnostic tool and people in neurosciences field and mental health and people interested in cognitive and behavioral disorders are starting to find that there are significant differences,

SPEAKER [FEMALE]:

at least in populations of subjects that are normal as compared to ones who exhibit particular symptoms of diseases. So you know we're hoping since we're in a developmental – developmentally oriented institute that we can really apply these approaches to look at developmental abnormalities, particularly in children. We have an activity in the lab where we're working to advance that very seriously. Carlo Pierpaoli again is involved in the pediatric neuroimaging project which is a consortium – supported by a consortium of institutes to obtain normal DTI data from infants from six months of age all the way to 18 years of age to be able to at least get a base line of normal diffusion data with which you can compare diffusion tensor data from subjects who have various abnormalities or diseases.

CW: And then the application would be screening of the entire population or what?

PB: Well I mean unfortunately the cost of DTI, the cost of MRI, is really too high in this kind of environment for screening, but if there are some technological breakthroughs in the next few years for instance that would allow you to do – build super conducting magnetic let's say out of liquid nitrogen as opposed to liquid helium or some people are starting to do imaging of low magnetic fields, maybe one day there'll be bedside MRIs that could be used in pediatric applications when children are born or possibly in intensive care unit. Under those conditions there could be significant screening applications. You know if every child were scanned you might be able to tell if the brain white matter architecture were normal and if the neuroanatomical substrates were all there and in the right – different pathways were in the right place at that stage of development. Certainly with genetic screening that's going on that could be done – maybe there could be some metabolic screening looking at abnormal levels of growth factors, things that might be able to be detected from blood tests, and then subsequent MRIs to be able to – you know that would be next level of screening that could be used to look at white matter architecture. Certainly it could be used by drug companies that are interested in neuro-protective agents or in the efficacy of psychotropic drugs that are being given to see if there are any long-term changes in white matter structure organization.

CW: That's really projecting into the future. So the reliability of the method there was a problem at the beginning, I think, actually from one of your papers that when [unintelligible] trajectory were not uniform it was more difficult to measure and you were getting a lot of noise. Has that been resolved?

PB: I think it's improving. There are some problems in tractography. You know we talked about tractography but we also talked about all of the blemishes and problems, you know the soft underbelly of tractography, and there are many problems with it. And some of them are being addressed, some of them haven't been. The imaging diffusion weight imaging data is now of a higher quality than it was even five years ago, much higher quality. The signal strength with respect to the noise is much greater. Certain artifacts like eddy current artifacts are being remedied to a larger extent. Motion artifacts are a little bit easier to correct for also in part to some of the efforts that are going on here in our lab to do better registration of MR data and some of these problems are being chipped away.

Now in terms of fiber tracking itself there are some topological problems that I'm not sure that DTI is ever going to solve. You know fibers that cross or that merge or that – we call it kissing. [telephone ringing] Oh that's my fax machine. It's not possible currently with the DTI data, or even more advanced models of diffusion that look at the apparent diffusion properties in many, many more directions to necessarily divide or determine the underlying topology without either using a priori information or some other methodologies that are complimentary that provide information that would allow you to tease apart those underlying topological differences. So we're confident for instance in the big tracks where – that run fairly parallel and that run by themselves and particularly in peripheral nerves it's very exciting because – the peripheral nerves are much more regular and there aren't that many geometric possibilities for them and there, I think, tractography will really come into its own in the next five years looking at things ranging from Carpal Tunnels Syndrome to problems in the spine. But in the brain there are regions like in the Pons sub cortical white matter where the white matter travels along and all of a sudden shoots out at a right angle towards the cortex. Following even white matter from gyrus to gyrus through sulci can be difficult because you don't know where individual fibers terminate and where they continue. So I think that there's a – you know the microstructure is so much more complicated than the macroscopic picture that DTI provides that I'm not sure that it's ever going to be sufficient for doing high resolution tractography, but I think that with maybe some other pieces of information that other imaging methods can provide and maybe from some neurological types of test that could be performed, you could start to eliminate some of these ambiguities and maybe connect one region to another and show that certain topologies that could be there can't actually be anatomically correct.

So I would say the tractography problem has – we've advanced the technology a lot particularly in diffusion weighted imaging technology – well not we, but I'm speaking about the field now. The companies have provided better sequences. There's been a lot more improvement. There've been improvements from the universities and hospitals and the underlying theory and the hardware and the software for acquiring diffusion imaging is better and some of the models are better now, but there's still underlying problems that DTI or any diffusion imaging approach aren't going to be able to solve with respect to tractography from where I sit now.

CW: [laugh] Yeah.

PB: Ten years from now who knows whether I'll even be in this field, but ten years from now I may have a different perspective.

CW: Well so what is W – DWI?

PB: Oh I'm sorry. DWI is diffusion weighted imaging. This is the technique which was actually prophesied or augured by Paul Lauterberg [spelled phonetically] back in I think 1973 in his famous *Nature* article, but was brought to life – brought to practice by a number of groups, Maribou [spelled phonetically] and others and Denis Le Bihan and Taylor and Bushell around the same time they proposed the possibility of producing images in which each voxel within the imaging volume were weighted by the local diffusion properties. So the intensity of the signal that you measured was related to the diffusion properties and all of them in their own way proposed formulas that you could us to in fact take that diffusion weighted imaging data and turn it into a measured diffusion coefficient in each voxel.

You probably should know that the measurement of diffusion using NMR go back really to the late 1940s / early '50s. The theory and the underlying experiments that are the basis of diffusion measurements with NMR are classical and quite beautiful work by Purcell and Carr and Hahn. Hahn realized that the spin echo could be affected by diffusion and Carr and Purcell actually in 1954 published the first measurements of diffusion coefficient using NMR and described as the most – what was the word? I think they used that it's – "One could not imagine a more non-perturbing measurement of diffusion." It was a very understated but somewhat self-congratulatory phrase at the end of the paper, but they realized that this was a really powerful way to measure diffusion without actually physically labeling the molecules, without introducing a new species and you were labeling the nuclear spins, which really didn't play a role in the chemical activity of the molecules. So this was a real breakthrough and actually Purcell won a Nobel Prize. I think in part for his – the measurement of the diffusion coefficient using NMR and then there was work in the mid-'60s.

The most important work was probably by Stejskal and Tanner who not only improved the hardware but came up with a more advanced theory of how you can relate the signal – the measured NMR signal to the diffusion coefficient and then you know there were – Mike Mosely and his group, I think there were two papers by Wesby, Eman [spelled phonetically] and Mosely which I think, as far as I can tell, were the first demonstration of diffusion weighted imaging where they not only showed the formulas but they also produced the images that were diffusion weighted. It suffered from a technical problem, which prevented it from being useful clinically, but it was that data that I think Le Bihan and Bushel and Taylor and Maribou were drawing from when they proposed a clinically feasible way of doing diffusion weighted imaging. In fact DTI uses those diffusion-weighted images with a new model and a new experimental design to extract new and useful data, the tensor and the quantities that you can derive from it. The various scalar quantities like the trace, which is used a lot in stroke assessment. A lot of people don't know that's a DTI quantity, but it is probably the most important one that we proposed and then there is the fiber orientation information in the vectors and then you have tractography which comes from looking at those fiber orientations in different voxels and following direction of maximum diffusion. So there's a lot of information that flows but the actual input is the diffusion weighted imaging data and the output is the tensor and the quantities you derive from it.

CW: So where are you going to go from now? What's your next project?

PB: Are you going to turn your recorder off?

CW: [laugh]

PB: No I'm kidding. Well in fact we continue to think that the diffusion sensitization provides new and useful information but we are moving away frankly from DTI per se because it's based on a very simple model of diffusion which works under clinical conditions right now extremely well, but as scanners are becoming more powerful gradients can be made larger, diffusion weighting can be made larger. We can start as you increase the diffusion gradient strength we can probe smaller and smaller length scales and you can start to see the effects of what's called constriction. You can see in fact what are populations that are probably trapped within axons and we are very interested in looking at different populations of water within brain and within other soft tissue which we really weren't able to see with DTI with hardware and software that we had available in the '90s.

So that's – there's a lot more information that is – you can glean from diffusion weighted data than we're currently getting. So one part of the lab you know activity is to improve our models of tissue microstructure and exchange of water from one compartment to another, and our ability to use at diffusion imaging to look at micro structural features that we really didn't think would be possible to do even three or four years ago. In fact I proposed in our last board of scientific counselors meeting a project that I would have actually laughed at myself four years ago. I never would have even considered doing it because it wasn't practicable, but now we want to be able to look at some microstructural features and we're confident that we can do it and we're also thinking about ways of measuring displacement distributions using a vastly reduced number of acquisitions. So that not just a tensor but other higher order parameters that we can measure that provide additional information about microstructure and you know possibly the number of sub compartments that may exist within a voxel, could be gleaned in about the same amount of time that we're doing DTI.

It won't solve the problem of tractography and the issue of fibers whether they're kissing or crossing – you know some of those topological problems, but it will give you an idea of how many distinct compartments you have, how much water you might have intracellularly as opposed to extracellularly. We actually have a patent application for some abstracts that deal with measuring the fiber diameter distribution in white mater. That's a micro structural quantity that's of great significance and I never would have thought that we could have done that even a few years ago, but it turns out that the models that we developed are very amenable to measuring it and we made some measurements in sciatic nerve, in optic nerve, in spinal cord and we get histologically very plausible fiber diameter distributions when we compare it to the histologic sections that we've done. So you know that could be important in a lot of development disorders, maybe ALS where large diameter fibers drop out early on in the process, particularly in the central nervous system it's very hard to make that diagnosis. Also development disorders, autism, because of the poor regulation of nerve growth factors that other groups in our institute have identified in autism, you know the up regulation and down regulation of nerve growth factors, I think there's a suspicion that the fiber diameter distribution is skewed in a pathological way in some of these neural developmental disorders, and I think it would be very exciting to use these new techniques there. So we're trying to push the envelope in terms of what we can see micro structurally, and there's so many creative biologists and physicians out there who once you give them a quantitative tool will apply it in ways that you couldn't have imagined, but then are delighted by the – I think that's going to spawn out another generation of developments that we're [ringing] – that was my email – that we'll be happy about. So those are the directions that we're currently moving in.

CW: Okay, great. Thank you very much.

PB: Well, it was my pleasure. I really had –

[end of transcript]