

John Tanner, the return to Germelshausen, and the work that nearly never happened

INTERVIEW BY **DEREK JONES** COVER PHOTO BY **TOM ROBERTS**

Toward the end of 2016, I felt honored to be invited by the editors of *Magnetic Resonance in Medicine Highlights* to interview John Tanner, Ph.D. With Ed Stejskal, John Tanner, invented the pulsed-gradient spin echo method, and conducted theoretical and experimental works that pushed the field of diffusion NMR forward, including the first use of the stimulated echo for diffusion NMR, and the use of restricted

diffusion NMR to estimate barrier spacing, true diffusion coefficient, and membrane permeability.

John kindly agreed to travel from his home in Idaho to Cardiff, UK, for the interview. Realizing that many people would be keen to hear Dr. Tanner speak, a two-day meeting was organised entitled, "A Spin Thro' The History of Restricted Diffusion MR", (Jan. 31-Feb. 1, 2017) assembling key innovators in the field from the last 50 years.

Dr. Tanner was the first speaker of the meeting, after which we chatted about his life and career.

What emerged was a story of a brilliant physical chemist who almost gave up on his research career, facing several challenges along the way, but who made a number of fundamental contributions to our field. It also became clear that until recently, Dr. Tanner was unaware of the huge impact that his work has had on the use of magnetic res-

John Tanner (right) and Derek Jones at the Cardiff University Brain Research Imaging Centre.





John Tanner in Cardiff, UK.



John Tanner at one year of age in Alliance, Ohio.

onance in medicine.

DKJ: Dr John Tanner, it's my pleasure to welcome you to the Cardiff University Brain Research Imaging Centre. Perhaps we can begin by learning about the early life of John Tanner?

JT: I was born in Cleveland, Ohio, in 1930, and subsequently raised in Alliance, Ohio. In my last two years of high school, I went to a small boarding school, where I found I liked chemistry. When I got home, I set up a small lab in my basement, bought a nine-pound bottle of concentrated sulphuric acid through the mail, and made ether and gassed myself on chlorine!

Then I went to Oberlin College, Ohio, majoring in physical chemistry. I had a family interest in German, and German was an important scientific language at the time, so I minored in German.

DKJ: After graduating, you did a master's thesis. What was that in?

JT: We were making precision measurements of specific heats of salt solutions to test the Debye-Hückel theory. I used a delicate, fragile apparatus that was very painstaking to use,

but I learned a lot about tools, about complicated soldering, and about precision electrical resistance measurements.

After my thesis professor died, I wrote to two others who had made measurements with the same equipment, suggesting we publish together. They wrote back and said in their lifetime as scientists this was the most exasperating research they'd ever done, one saying *"Those lead wires would break if you just looked at them crosseyed"*.

DKJ: But that experience probably stood you in good stead for your later electronics work. On completion of the Master's, what happened next?

JT: I had accomplished at least one set of measurements, but I got tired, and wondered if this was what research was really like. I was tired of research, and so I volunteered for the draft (U.S. Army). I went to the Army Medical X-ray Technician training school, and was stationed at hospitals in Germany. So I became familiar with every fossa and protuberance of all the bones in the body!

DKJ: So, after you completed your service in medical imaging, unaware that your future work would have a huge impact on imaging the body, what did you do next?

JT: I got admitted to the University of Wisconsin graduate school, and spent two years doing course work. One professor suggested a research project, but I immediately did an experiment to show that his idea wouldn't work! I was a little bit tired of things so I took a job at a research laboratory outside of town. Their major focus was on physical chemistry of the rapid freezing of solutions related to preserving bull semen. I did a number of experiments studying the colligative property of gelatin in solution and interpreting patterns of rapidly freezing salt solutions. The boss was interested, but then decided I had done enough of that.

DKJ: So, what was the route to your Ph.D.?

JT: I'd started taking courses again at the University (while at the nearby private research lab), and decided to continue with a Ph.D. I interviewed all over the department and chose Ed Stejskal to work with. I was interested in diffusion, Ed had a magnet and I knew about the spin echo method of measuring diffusion coefficients. I thought it was a neat method, partly because sample preparation was pretty simple once you had the equipment, and the experiments didn't take very long.

DKJ: So you were familiar with Hahn's paper

as a potential method for measuring diffusion, but there was a problem, wasn't there? Inspired by your previous work on gelatin, you wanted to look at samples with very low diffusion coefficients?

JT: Yes, I wanted to study the relation between viscosity and self-diffusion of water in gelatin solutions, which involves viscous solutions with low diffusivity, which in turn would require much stronger gradients with the Hahn method.

While I was building my gradient coils, Ed was thinking about the problems I was going to run into, and had his midnight brain storm that I ought to apply the field gradients in pulses, instead of continuously, to avoid the problem of having the RF pulse not cover the frequency spectrum of the solution as you go to higher and higher field gradients.

DKJ: Yes, you told me that at one a.m., Ed left a note for you before he went home, complete with some finely crafted calligraphy:

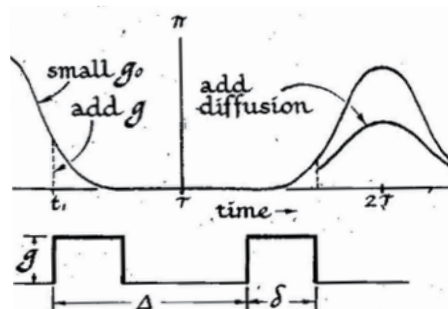


Figure 1. Illustration from the midnight brainstorm by Ed Stejskal.

JT: Yes, and he left a sketch of a transistorized amplifier that we could attach to our pulse generator.

DKJ: So that was the origin of the pulsed-gradient spin echo. But the aim at the time wasn't what we now know as the main application of the sequence. To quote you from your 1965 paper, *'In an attempt to eliminate some of the experimental limitations mentioned above, we have developed a technique in which the field gradient is considerably reduced during the times at which the RF pulses are being applied and also at the time of the appearance of the echo.'*

You were really trying to solve a problem, of how to measure low diffusion coefficients, and you realized that Ed's suggestion would open new possibilities for your research.

JT: Yes, but I didn't realise that our pulsed-gra-

dient method was going to be useful for an even more important purpose until I started designing the amplifier. I started asking myself about timing of the pulses, and thinking about the motion of the spins and what that might have to do with any timing requirements. It was then that I had a key insight. I realised that any diffusion motion would have the same effect regardless of where it happened between the pulses. It didn't really matter how the pulses were spaced, as long as the two were on opposite sides of the 180 RF pulse, and their magnitude was equal. You couldn't say the same thing about motions that happened during application of a steady gradient, or within a gradient pulse. In that case, it would depend on where within the gradient time the motion happened, but by making those pulses narrow compared to their separation, you could have a clean experiment and 'the time during which the diffusion process is being observed is precisely defined'.

DKJ: You've also told me that you were inspired by Don Woessner's work? (Woessner DE. NMR spin-echo self-diffusion measurements on fluids undergoing restricted diffusion. *J Phys Chem.* 1963. 67:1365–1367.)

JT: Well, I thought it was interesting that by varying the diffusion time, you could see the effect of barriers. The question was how would you actually analyse that to get a quantitative estimate of barriers, and I thought 'Well this looks kind of complicated.' (Ed had the same feeling, and had also thought about going into this problem, but decided against it!) But I realized that with precisely defined diffusion times the mathematical analysis should be much simpler.

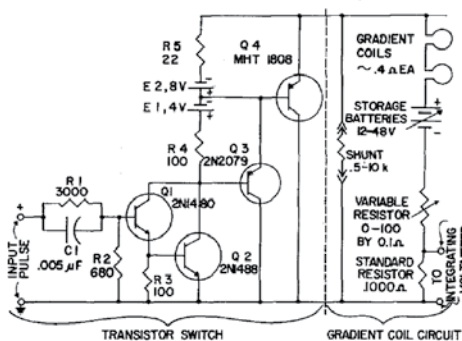


Figure 2. Transistor switch and gradient coil circuit. Resistance values are in ohms. (Tanner JE. Pulsed field gradients for NMR spin-echo diffusion measurements. *Rev Sci Instrum.* 36:1086–1087.)



Family portrait taken in 1980.

DKJ: But back then you couldn't just order a pulsed-gradient amplifier from a catalogue, so you had to make your own amplifier?

JT: Well, Ed had sketched the circuit diagram for a simple two-stage amplifier. Of course, he hadn't included all the little features and resistors needed to make it work right, and so I had to work that out myself. Then after I had done the preliminary experiments testing the theory, I wanted to go to more viscous solutions, so I enlarged the amplifier to four

stages and designed that.

DKJ: But with no background in electronics, how did you know how to construct this circuit?

JT: I was self-taught. I read about the properties of various transistors and what you needed to do to make the circuitry work.

DKJ: So you'd made the kit, and you then needed to quantify the effect of the gradients and the timing on the signal.

JT: By that time Ed had worked out the theory of the signal attenuation from the Bloch-Tor-



Former Ph.D. advisor, Edward O. Stejskal, and joint namesake of the Stejskal-Tanner equation.

rey equations. He derived the equation where the log of the echo attenuation is proportional to, amongst other things, three parameters - gradient strength, gradient length, and separation between the gradients. What I did was to test variation of each of those independently on a water sample and showed that no matter what you varied and how you varied it, it still obeyed that relationship.

DKJ: That relationship is what we all now know as the “Stejskal-Tanner equation:”

$$b = \gamma^2 G^2 \delta^2 \left(\Delta - \frac{\delta}{3} \right)$$

which you had now verified experimentally in fluids.

Did you have any impression of the impact it was going to have, beyond those initial physical chemistry arenas?

JT: Besides the restricted diffusion studies I made, I figured people would want to measure other things using the idea. I thought there would be a lot of systems (some biological, some mineralogical) with barriers of colloidal dimensions that people would find interesting, so there ought to be a number of studies of that sort of thing over the years.

DKJ: That brings me very nicely onto your 1968 paper “Restricted Self-Diffusion of Protons in Colloidal Systems by the Pulsed-Gradient, Spin-Echo Method,” where you discuss the benefits of measuring restricted diffusion using the pulsed-gradient. Equation 3 stood

out to me. Here you have effectively written down the q-space formalism. Although it wasn’t explicitly referred to as a reciprocal Fourier relationship at this point, it’s fair to say this was the first time it was written down. It has since turned out to be incredibly important in the medical literature, and was ahead of its time.

JT: I’d have thought this was something pretty obvious. It’s just integrals of things that you do in heat flow analysis.

DKJ: That’s a nice link into the various systems considered in the paper, borrowing models for the propagator from heat flow literature to look at diffusion in laminar systems. You started off with a mica stack?

JT: Yes, 99 layers of mica spaced by strips of aluminum foil. After designing it so I could accurately observe restricted diffusion, it took me two weeks to build it. I had to smooth off all the wrinkles in the aluminum foil and scrape burrs off the mica, so that it would be very even. Ed used his stereomicroscope to look at it and said he was surprised how regular the spacing was.

DKJ: You then derived what I believe were the first ever examples of analytical models for the diffusion signal in restricted geometries. Many of these have been since carried forward to applications in biological systems. Your next big innovation was looking at anisotropic and restricted diffusion, but with very long diffusion times, without suffering excessive T_2 relaxation.

JT: Yes, using the stimulated echo method, which I’d read about in Hahn’s paper. The triple-90 RF pulse method looked attractive

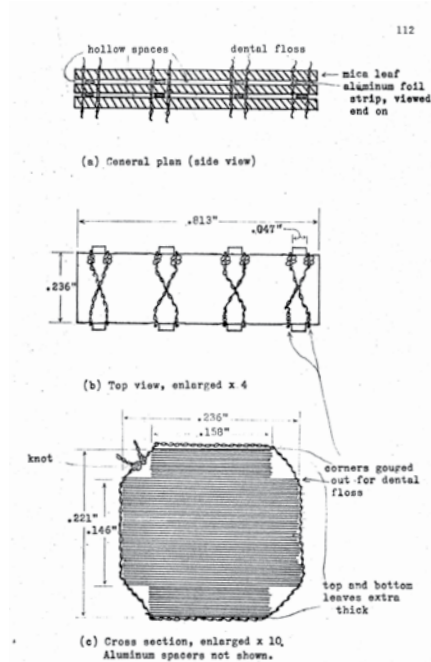


Fig. 27. Mica sheet stack for restricted diffusion measurements.

Figure 3. Diagram of mica stack, aluminum foil, and dental floss used for experiments on restricted diffusion.

because you could have a long space where signal decay was only due to T_1 instead of T_2 . You paid a penalty at the start with a loss of 50% of the signal, but in cases where the T_1 / T_2 ratio was large enough, it was worth it.

DKJ: Did you encounter any problems with implementation?

JT: The main problems were in the first use of the pulsed-gradient, with all the battery recovery times, and the drift of the analogue pulse-generators. So I had to watch the echo and make sure it happened at the right time.

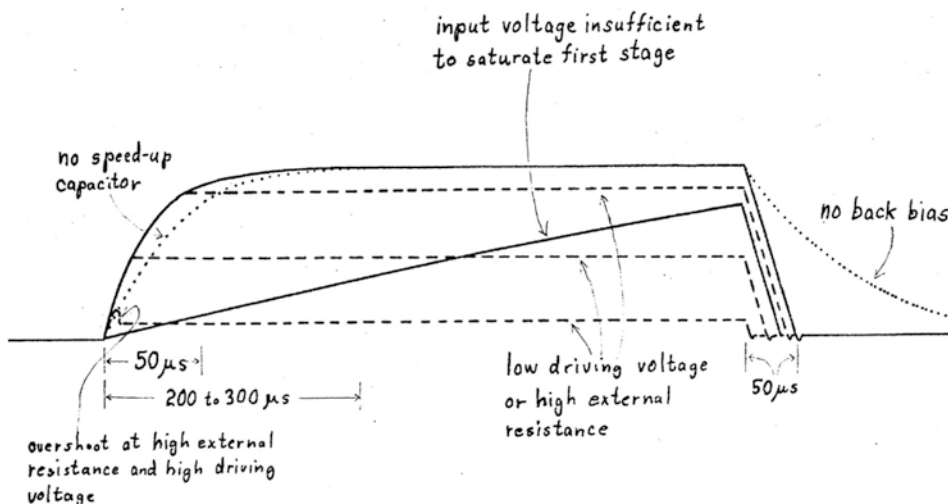


Figure 4. Hand-drawn figure of the gradient pulse design used for diffusion measurements.

There were also problems with eddy currents with tails lasting several milliseconds. I had to resolve this by redesigning the probe.

DKJ: At the time you were doing this work, what were the social pressures on funding for research? And how did they impact your research career?

JT: Well, there was a real love affair with science in general after the Russians had sent up their first Sputnik, and we failed in a couple of subsequent attempts to do the same. People said we needed more trained scientists, so science got heavily funded for a while. But toward the mid-1960's, people began to doubt whether they were getting their money's worth. Things began to change and companies started actually laying off scientists. It was a tough time to do job hunting and that was right when I was on the job market.

DKJ: You found it hard to find a job?

JT: Oh indeed!

DKJ: So where did you end up?

JT: After a few postdoctoral appointments I was employed at the Naval Weapons Support Centre at Crane, Southern Indiana, doing research on pyrotechnics, smoke, illuminating flares, and decoy flares. I may have made some fundamental steps forward there, but I would not be allowed to know whether there was any follow up.

DKJ: Well, what we are allowed to know is that, while there, you wrote another theoretical paper entitled "Transient Diffusion in a System Partitioned by Permeable Barriers."

JT: On the side, I was allowed to apply for funding to do more NMR diffusion work. Some of it was theoretical, and some experimental, where I rented equipment at nearby Indiana University. That was where the frog muscle paper was done.

DKJ: That paper, "Self Diffusion of Water in Frog Muscle", is one of the earliest to apply a whole series of pulse sequence designs to the study of biological systems. The paper shows you using oscillating gradients, pulsed-gradient spin echo and stimulated echo in the same experiment (Figure 5). There's been a resurgence of the use of oscillating gradients to study cell sizes as you heard over the last two days at the conference. But the Naval Weapons Support Centre allowed you to study frog cells. Was there a plan to deploy frogs as weapons?

JT: No. It was just that we were not an official lab, so we had to apply for grants. My boss told us to get whatever money we could for



Backpacking in Glacier National Park during his time as a graduate student.



John Tanner with his grandson.

whatever purpose.

DKJ: What were the key results from the frog muscle paper?

JT: Well the measurements were made perpendicular to the long axis of the muscle, and I showed that generally the diffusion coefficients at shorter diffusion times, where the barriers weren't apparent, were somewhat less than pure water due to the various obstacles along the way, but the obstacles were too close to observe a specific effect, so more like the obstacles of a viscous solution. They were about 20% lower than the diffusion coefficient of free water due to the finely spaced barriers. I was then able to detect barriers separated at larger distances, which apparently were the cell wall boundaries. I was also able to make an estimate of the cell wall permeability using the theoretical work I'd done on permeable barriers. Apparently it was useful, because I got a lot of postcard reprint requests.

DKJ: So was that your last paper in diffusion NMR?

JT: Yes, that one and another paper in *Archives of Biochemistry and Biophysics* on a few more cell samples from various professors. I left for Idaho before I could finish everything.

DKJ: Looking over a relatively compressed research career in diffusion NMR, could you reflect on the piece of work that gave you the biggest 'Eureka!' moment?

JT: I suppose the biggest eureka moment was realising that this pulsed-gradient method was a cleaner experiment with a good definition of the diffusion time (as we later called it), and that the analysis of restricted diffusion would be much simpler and cleaner, so there'd be a lot of things you could do with it. It was then that I totally gave up on the idea of the gelatin solution viscosity problem.

DKJ: Your last diffusion MR paper was in 1983. What has happened since then?

JT: Well after the pyrotechnics work, I moved to Idaho. I was part of a two-year project developing a method for long-term storage of radioactive krypton by compressing it into a zeolite and then sintering that zeolite. But the project ended as we realised that there wasn't much krypton to be disposed of and there was big industrial demand for whatever there was left. My remaining 15 years were in criticality safety, doing mostly Monte Carlo calculations on various operations to avoid unintended criticalities with the highly enriched weapons-grade uranium we were using. That

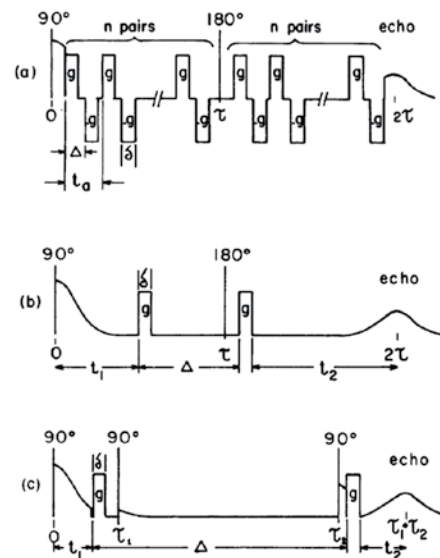


Figure 5. Radio frequency (900, 1800) and field gradient (g , $-g$) pulse sequences suitable for diffusion measurements at (a) short, (b) intermediate, and (c) long diffusion times, respectively. (Tanner DE. Self diffusion of water in frog muscle. *Journal of Biophysical Society*. 1979. 28:107–116.)

was interesting, I did miss the lab work, but I enjoyed the calculations too.

DKJ: How are you enjoying your retirement?

JT: I've always been interested in gardening. But one of the major things my wife and I have gotten into is advocacy for treatment of the mentally ill. Our younger son was talented in organic chemistry, but developed schizophrenia. We had a rollercoaster of a time ensuring that he received the care he needed. We've since been involved with legislators, forwarding them information from medical journals, and now sit on several statewide committees on this topic.

DKJ: You've been out of the field for quite a while. Last year, the ISMRM awarded you Honorary Membership and you came along to your first ISMRM! Reflecting on this prompted you to tell me a German folk story.

JT: Yes – Germelshausen. Well, I was in an environment that was totally out of magnetic resonance and diffusion, and not much into deep science. Then spending a few days at the ISMRM, I was back in the kind of environment I was in 40-50 years ago before heading back to my old environment. Now suddenly in Cardiff, I'm back into this environment once again. This reminded me of an old German folk tale, about a village, Germelshausen, which existed for just one day every 100

years. At midnight it disappeared, and was pasture again, until the next 100 years.

DKJ: Well you re-entered the diffusion Gernshausen a couple of days ago, and you were our first speaker at our celebration of the history of restricted diffusion MRI. You got to hear your name many times during the meeting. I kept looking across and saw you smiling. I wondered how you felt? This work, that you started off nominally to remove an obstacle to measuring low diffusion coefficients, has since had huge impact, leading to early diagnosis of ischemia, allowing people to navigate and resect tumours – the full gamut. How does it feel?

JT: I hadn't thought of all of that. I was amazed, of course, looking over the program of the ISMRM. In fact, at the ISMRM, one of the guys saw my nametag and said, 'So you're the guy who put us all to work?' It floored me, it really did.

DKJ: Well, I'm incredibly grateful to you for putting me to work, and there's thousands more people around the world who are grateful to you for putting them to work.

JT: Well I did the research for fun. Not to benefit someone. It was just fun.

DKJ: Well John, it's been great fun talking to you. Thank you for the interview and on behalf of the entire diffusion MR community, thank for your seminal contribution to our field. ■

Interview has been lightly edited for clarity. A video of the entire interview can be found at: www.youtube.com/watch?v=ixu6I7eJZEc

Derek Jones

Prof. Jones is Fellow of the International Society for Magnetic Resonance in Medicine (ISMRM) and the Royal Society for Biology (FRSB). He has held various positions within the ISMRM including Programme Chair of the ISMRM Annual Scientific Meeting in Milan, 2014, has twice been Chair of the Diffusion Study Group, and served as Deputy Editor for Magnetic Resonance in Medicine. He has published widely on all aspects of the diffusion MRI pipeline, from data acquisition through to applications, and edited the book 'Diffusion MRI: Theory, Methods and Applications' – to which Dr. Tanner contributed his personal reminiscences together with Ed Stejskal. Prof. Jones is Director of the Cardiff University Brain Research Imaging Centre (CUBRIC) in Wales, UK (<http://sites.cardiff.ac.uk/cubric>) and his research is supported by the Wellcome Trust, EPSRC, MRC and Wolfson Foundation.



John Tanner, and his wife of 50 years, Martha Tanner, MD.