Putting fertility research into motion

Allan Pacey is Professor of Andrology and Head of the Department of Oncology and Metabolism at the University of Sheffield, UK. He was previously Chair of the British Fertility Society from 2012 to 2015 (the first non-clinician to hold that post) and is currently Editor-in-Chief of their official journal Human Fertility. Professor Pacey has recently worked with the World Health Organization, and is active in public engagement activities around both fertility and cancer. He was awarded an MBE in 2016, for services to Reproductive Medicine. Science Editor Chris Willmott spoke to him about his work.

Thank you for sparing the time to talk to us. Can I ask you to begin by telling us about your own journey into the field of fertility research?

I grew up in rural Yorkshire in the 1970s and it’s true to say going to university wasn’t the kind of thing that rural boys did at the time. So, in modern parlance, I’d now be seen as a “Widening Participation” success story. In fact, I only applied to university because my best friend did. I went to study life sciences at the University of Hull. It was whilst I was there that I got really fired up about reproductive biology.

What was it that triggered your interest?

I think there were three things. The first was reading all 5 volumes of Roger Short’s textbook on Reproduction in Mammals in the Hull University library where, incidentally, the poet Philip Larkin was still head librarian; we would see him walking around. The second was the influence of an inspiring young lecturer John Robinson, who went on to set up the Hull IVF centre. The third was reading the Warnock report [The 1984 Report of the Committee of Inquiry into Human Fertilisation and Embryology, chaired by Mary Warnock], which struck me as a well-written and thoughtful paper.

So what was the next step?

After Hull I went to St Andrews to do my PhD, under the supervision of Matthew Bentley. At that stage I still didn’t have an active interest in human infertility; the research was in cell biology, specifically on sperm maturation in the lugworm. This led into a Royal Society research fellowship which allowed me to spend a year at a research station near Nice, in France. I was still working on the lugworm but also sea urchins as well. The main focus was on the influence of calcium on sperm movement. I didn’t clone any channels or anything like that, but we did make some significant observations, including stumbling onto the importance of certain wavelengths of light in directing the movement of these sperm.

From France, you went to Sheffield, where you still work?

Yes, that was the point at which my direct interest in human fertility began. The team in Sheffield were interested in how sperm behave in the female reproductive tract, or rather in model systems of it. I worked with clinical staff for the first time, consenting women who were undergoing hysterectomy in order to obtain Fallopian tube cells to culture in the lab. We did make some discoveries, but the work was eventually abandoned because it fell out of fashion. However, not before a certain amount of press coverage.

An aeronautical engineer at Glasgow, Richard Green, saw something on TV about the work I was doing and recognized that there was potential overlap with the kind of studies he was doing in aeronautical engineering (using fluid dynamics). This led into a very fruitful partnership in which we were able to show much more clearly than previously how the movement of the flagellum achieved the swimming motion of sperm.

Jumping to the present, what is the focus of your current research?

I’m still working on improving our understanding of aspects of male infertility, including the basic biology of human sperm. We have some very promising work developing an NMR-based screen for sperm health. At the moment tests for sperm quality are destructive, it’s like saying “oh, that was a good one” by which time it is too late. We are studying live sperm using various methods of magnetic resonance spectroscopy. The fundamental principles are the same as those involved in an MRI scan, so we are confident the technique is safe to the sperm.
Sperm need to generate ATP to sustain movement. The tail and mid-piece of sperm are relatively rich in enzymes associated with lactate metabolism, but there has been debate about the relative roles played by glycolysis within the cytosol and oxidative phosphorylation in the mitochondria. The kind of NMR we are doing doesn't provide structural information, but as we follow the processing of molecules like $^{13}$C-pyruvate we can get ‘snapshots’ of the relative proportions of metabolic intermediates. This gives us a handle for looking at differences between healthy sperm and poor swimmers, and the influence of local conditions on motility. The test isn’t instantaneous but, as I said, it is non-destructive and, of course, sperm are fairly robust since they may take up to 6 days from ejaculation before they reach the egg. If you want to know more, we have a SPERM research website dedicated to this aspect of our work (http://spermnmr.group.shef.ac.uk).

Alongside your scientific and clinical research, you’ve been heavily involved in some groundbreaking TV programmes about fertility. No-one who has seen the Great Sperm Race (2009) will forget the image of thousands of men and women in white boiler suits charging down a valley and up a staircase as they recreated the journey of sperm seeking an egg. Can you tell us a bit about how that came about?

The first thing to say is that there wasn’t really a cast of thousands, there were only about 25 actors, the rest was CGI trickery. The evolution of the Great Sperm Race is actually quite interesting. In 2006 I’d published a review article with Susan Suarez in the journal Human Reproduction Update. A young TV producer read the review and contacted me about the possibility of making a documentary. She made a pitch to Channel 4 and managed to secure some funding from the Wellcome Trust. The programme was very well received around the world and I still get emails about it. Last time I checked it had been shown in 24 territories around the world and had been seen by over 10 million people. It also spawned an online game, which is still available and has been played over 30 million times. The project was one of Sheffield’s Impact cases for the last REF.

As you are aware, this issue of The Biochemist is timed to mark the 40th anniversary of the birth of Louise Brown, the first IVF baby. What
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would you say were the most important two or three developments in Assisted Reproduction Technology over that time?

Clearly, if I'm allowed, I’d like to choose the original pioneering work of Patrick Steptoe and Bob Edwards. They really didn't get the credit they deserved at the time. Edwards eventually received the Nobel prize in 2010, but Steptoe had died in 1988 and therefore missed out.

As a second choice I’d say the invention of ICSI – intracytoplasmic sperm injection – in which a single sperm is injected directly into the egg. This has been revolutionary for cases of infertility where the problem lies with the male partner.

Are there aspects of fertility treatment that concern you?

There are lots of things that are potentially worrying. Couples seeking help to conceive are incredibly vulnerable emotionally, and there are dangers that they will get exploited by unscrupulous clinics conducting procedures that won't really help, so called add-ons. Take the use of ICSI, which we mentioned earlier. In the UK roughly 50% of IVF treatments involve ICSI and since about half of infertility arises from the male partner, this seems reasonable. But in some parts of the world ICSI can make up over 90% of IVF procedures, and that doesn't seem right.

Better funding of fertility treatments on the NHS in England would help to guard patients against this, because the clinics they'd go to would have to follow the NICE guidelines (funding in Scotland is different, and more generous).

What would you say is the biggest unmet need in current fertility treatments?

At the moment we don't have any treatments for male infertility, only work-arounds such as ICSI and freezing of sperm when a decline in fertility is predictable (e.g. for people undergoing certain chemotherapies or for soldiers involved in front-line combat). In some senses, the success of ICSI has unhelpfully shifted the focus away from understanding and dealing with the underlying biology of the problem. If we knew why some sperm were immotile and how we could revive them, then it might be possible to develop a compound delivered as an ointment or a lubricant, which would allow them to swim. If this then allowed couples to conceive without IVF or ICSI then that could save them a huge emotional and financial burden.

Professor Pacey is an enthusiastic tweeter. To keep up to date with his work, please see www.twitter.com/allanpacey

Further reading, viewing… and gaming

- Spectroscopic Probes of Energy Regulation and Metabolism (SPERM research) http://spermnmr.group.shef.ac.uk
- The Great Sperm Race documentary. A copy is currently available at youtu.be/Fda5rigma14