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INTERVIEW

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Interview with Professor Morris Brown

Morris Brown*

Morris Brown is Professor of Clinical Pharmacology at the University of Cambridge, UK. He is currently running three British Heart Foundation trials. The focus of his research is hypertension, with a particular focus on the adrenal causes of hypertension. Prof. Brown was awarded the Lilly Gold Medal of the British Pharmacological Society in 2002, the Hospital Doctors' Award in 2003 and in 2006 received the Walter Somerville Medal of the British Cardiac Society. He recently spoke to *Clinical Investigation* regarding changes in his field, the regulatory landscape and the future of clinical trials.

Interview conducted by Alexandra Hemsley, Commissioning Editor.

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Q How did you become interested in the field of hypertension?

I became interested many, many years ago when I was a junior doctor at Hammersmith hospital in London. I was working under Professor Colin Dollery; hypertension was his interest and he got me interested in the subject.

Q How did you get involved in large scale clinical trials?

I was involved in small trials when I was at Hammersmith, working in the Department of Clinical Pharmacology. I conducted some of the first-dose-in-man studies of the new classes of drugs for hypertension, such as ACE inhibitors and calcium blockers, and then I started to conduct larger studies after I moved to Cambridge. In the late 1980s and early 1990s, there was a complete information gap concerning the long-term efficacy of the newer drugs. I had been involved in recruiting reasonable-sized cohorts of patients and I was interested in going to the next step of recruiting them into trials to look at the long-term benefits of treatment. This culminated in the INSIGHT study, which remains, to this day, the only double-blind outcome comparison of the two most effective drug classes in older patients, calcium blockers and diuretics.

Q How has the field changed over the last decade?

The large trials mentioned above, of which the majority were completed by 2005/2006, provided an enormous amount of evidence that – for a given fall in blood pressure – all the classes we have for treating hypertension are equally effective in preventing complications, heart attack and stroke. The second half of the decade has brought us back to what, in a way, has been my main interest: the question of how in individual patients we should be finding the optimal treatment. In 1999, when I started doing rotational studies in which the same patient receives

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in random order each of the drugs being compared, which led to the AB/CD rule later adopted by NICE, such studies were regarded as flaky and there was official skeptism that patients differed in their responses to different drugs. Now, 'personalized medicine' or 'stratified medicine' are mainstream and choosing the right drug for the right patient is essential across the breadth of Medicine.

Q Were there any unique challenges during the ACCELERATE trial?

It is always a challenge to recruit 1000 patients reasonably quickly. In a trial, you also have to decide in advance what your various criteria are going to be for recruiting patients and then you have to stick with them once you have started. What we did not know before we started the ACCELERATE trial was how well tolerated the combination of treatments would be from the outset. What the trial was testing was whether starting with a combination of treatments would be preferable to the convention of starting with one drug and then moving on to a second. The reason why that has not entered routine practice – despite cautious recommendation by both US and European guidelines – has been doctors' nervousness about causing excessive side-effects, and the assumption that use of two drugs would double the risk of side effects compared to using one. In the event, we were pleasantly surprised that not only did we not have more side effects in the combination group, we actually had fewer. Although we cannot prove it, we think that our hypothesis was correct, in that just using one drug you set up what is called compensatory responses, making the second drug less effective. Some of these compensatory responses are what causes the side effects and if you use two drugs together, they not only help each other work, but they actually block each others' side effects; so it is a sort of win–win.

Q Were any particular difficulties encountered during the PATHWAY trials?

PATHWAY is an ongoing program of three trials, undertaken by eight of the most experienced clinical investigators in the British Hypertension Society, and funded by the British Heart Foundation and National Institute of Health Research's Clinical Research Networks. Clearly, there are challenges to conducting three trials simultaneously. However, we thought that compensating the logistical problems recruitment would actually be easier, because we have deliberately spanned the breadth of hypertension between patients who have never been treated, through to patients who are on multiple drugs and are still not on target. Therefore, any patient who is not on target on whatever they are taking is broadly eligible for one or other of the three studies, which makes the recruitment visit more satisfying for both the patient and for us, because we can usually enter them into one of the three trials.

Q Have the trials exploring renin measurement in the routine management of hypertension led to changes in clinical practice?

This is one of the main questions that PATHWAY is addressing. We will not have a definitive answer until the trials have finished, but we are conducting the trials because there was already a lot of circumstantial evidence that knowing renin levels can and should influence treatment. The fact that PATHWAY has been quite a high-profile group of trials has already made many doctors, in both primary and secondary care, more aware both how easy it is to measure renin and, with almost weekly examples, how knowing renin levels influences patients' management. As well as helping choice of treatment, plasma renin is the most sensitive way of detecting approximately 5% of patients with hypertension in whom there is a curable cause.

Q Has the regulatory landscape for clinical trials changed in recent times? Are there any changes you would like to see implemented?

The answer is definitely yes. Unfortunately, since 2004 when the EU Clinical Trials Directive was implemented, this country's response to that, which I am told is not unusual in response to European legislation, is somewhat over the top and has made it very difficult for trials to be launched and run. Setting up PATHWAY was quite a severe learning exercise for us. I have been conducting clinical trials for the last 30 years and it was a bit of a shock to the system to discover what was involved for PATHWAY compared to everything prior to this. Because PATHWAY was a set of trials involving drugs that have been around for 25–50 years, and they have been conducted by the most experienced specialists in the field in the UK, they are incredibly low risk. Patients are at a much lower risk taking part in these studies than they are in every day life. Furthermore, we know already that of these previously uncontrolled patients, more than 70% do come down to target during the course of the trial. It is very frustrating to have so many delays; so much of our time and effort spent completing paper work that just does not contribute to the benefit of doing research. Although we all had great hopes that the Rawlins review last year would change things, our perception is actually that things have got worse. The main obstacles are the R&D departments who are actually not even mentioned

in the legislation, which means that, unfortunately, they make up their own rules and that they are not bound by timelines or ethics. Following the Rawlins review, there has been a decision, which I do not think was widely publicized, that trusts should be penalized if their R&D departments do not let their departments start research within 70 days. However, what we are finding is that some trusts simply move the goalposts, and simply impose the delay before you can even apply to ethics and do not start the clock until after that delay is over. Even after ethical approval has been received, our R&D finds a way of delaying the 70-day clock, and we are still waiting, for example, for R&D approval for a 12-patient pilot study conceived 1 year ago, for which ethics approval was received 4 months ago. Unfortunately, complaints regarding the delays, even from a senior Professor, attract the sort of bullying Trust retaliation that has been in the news of late. The business of starting research, and something I do running a translational medicine program for the Wellcome Trust, trying to teach young people to do clinical research by conducting small projects as part of an MPhil or PhD, has become almost impossible and that is very sad at a time when there is so much UK Plc money available for conducting clinical research.

Q How do you see the future of clinical trials progressing?

The UK is in many ways the ideal place to be conducting trials because of the amount of funding available, because of the set up within the National Health Service where each patient has a unique record that can be tracked, and the increasing ability to obtain long-term data on outcomes on a patient, without necessarily having to see them again. However, we do need to get away from the culture where there are more people involved in creating obstacles than there are people solving them. We also really need to be attracting some of the brightest academics into going into clinical research, rather than going straight to the laboratory bench and working with molecules and DNA.

Q What advice would you give to someone considering a career in clinical research?

If they can bear to cope with the things I have described above, ultimately clinical research is where the real excitement comes. I have been lucky in that I have been able to tread a path that allows me to combine molecular and clinical work. And in one specialized area, our work on adrenal gland causes of high blood pressure has enabled clinical and research expertise to become perfectly intertwined, with the same patients benefiting from, and contributing to, research into the molecular basis of their hypertension. Each patient is an experiment of nature and gives clues about what molecules to look at. The clinical expertise is in recognizing the differences and similarities between patients, and in applying the fruits of the research. Most diseases are much more complex than previously thought. Although it is becoming increasingly straightforward to identify specific molecules and mutations contributing to the disease, the proof of their involvement, and value of their discovery, depend ultimately on the molecule becoming a target for new and successful therapy. I hope that the new young clinical academics will be switched on to wanting the excitement of seeing hypotheses tested in patients, which is more satisfying in the end than doing them in individual cells or experimental models.

Disclosure

The opinions expressed in this interview are those of the interviewee and do not necessarily reflect the views of Future Science Ltd.

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