Some thoughts on the future of stroke

David Blacker speaks to Simi Thankaraj, Assistant Commissioning Editor

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David Blacker was born in Bunbury, Western Australia, and studied medicine at the University of Western Australia (Perth, Australia), graduating in 1991. He undertook physician and neurology specialist training in Perth. He developed an interest in acute stroke therapies early in his career, and was involved with cases treated with intra-arterial techniques in the mid-1990s. Like many young Australian neurologists, he then undertook 2 years of fellowship training at the Mayo Clinic (MN, USA). There, Blacker was mentored by Professors Bob Brown and Eelco Wijdicks, and further developed interests in stroke and acute hospital-based neurology. His return to Australia in 2003 coincided with the approval of tissue plasminogen activator as a stroke therapy. He helped establish the acute stroke team at Sir Charles Gairdner Hospital (Perth, Australia), and has continued to work on the development of stroke services locally, and across the geographically enormous state of Western Australia ever since. In his role as a Clinical Associate Professor of Neurology at the University of Western Australia, he is actively involved in teaching, and has a wide range of research interests mainly in acute stroke, but also in neurorehabilitation. In this interview, he shares some thoughts on the future of stroke treatment and research.

Interview

Future Neurology

■ Could you tell us a little about your career to date & how you came to your current role?

I have always been interested in neurology. I think it is the most interesting aspect of medicine and I cannot believe why my colleagues, working in other specialties, go past the brain in terms of interest! I completed a neurosurgical rotation for 3 months as an intern at Sir Charles Gairdner Hospital (Perth, Australia), which I loved because I found it fascinating; I worked more than 100 h a week. I then started a rotation in neurology (also at 'The Gairdner') and it was about the time when there were a few key pivotal stroke trials, such as the Australian Streptokinase Trial, which was negative, but demonstrated that stroke patients could be assessed and treated rapidly [1]. People started to realize that stroke was something we could possibly do something about. The cardiologists had, of course, been using thrombolytic therapy for myocardial infarction for some years; however, it was just starting to be investigated for stroke treatment and, therefore, I became interested in that.

Between 2001 and 2003, I completed two fellowships at the Mayo Clinic (MN, USA) where I studied many cases of stroke. In the following months when I returned to Australia, thrombolysis was approved for use as a therapy for ischemic stroke and it was getting underway

in clinical practice, so it was very good timing. This meant that we could set up an acute stroke service; this happened exactly 10 years ago.

■ What is your research focusing on at present?

At the moment, my main research interest is in making thrombolytic therapy safer. My colleagues and I have been interested in minocycline, a long-used antibiotic, for some years now, and have recently published a pilot study and meta-analysis of minocycline used to treat stroke [2]. Minocycline has been reported to have neuroprotective properties, which have been studied in a number of research fields for quite some years. What has interested myself and others in my group is that there are promising animal data suggesting that minocycline reduces inflammation, reduces edema and, most importantly, it seems to reduce the chances of hemorrhagic transformation in animal models of stroke treated with tissue plasminogen activator (tPA) [3,4]. The supposed mechanism of action of is that it reduces expression of inflammatory proteases in the vascular walls. Taking this observation into consideration, our current study, the West Australian Intravenous Minocycline and Thrombolysis Stroke Study (WAIMATSS) is looking at patients who are routinely treated

with intravenous tPA [5]. They are then randomized to intravenous minocycline in addition to tPA or to tPA alone. It should be noted that this is a small pilot study; however, we are using it as a paradigm to improve the safety of tPA and to work on reducing hemorrhage rates.

We are involved in a number of other collaborations at a national level, as well as smaller studies with local groups, including physiotherapists, clinical psychologists and speech therapists, all conducting clinical stroke research. One of my esteemed colleagues Graeme Hankey (Sir Charles Gairdner Hospital and the University of Western Australia, Perth, Australia, previously at the Royal Perth Hospital, Perth, Australia) is involved in large study on fluoxetine for stroke recovery that we are participating in [101].

■ **What novel treatments for intracerebral hemorrhage are on the horizon?**

I feel that this is an untapped area. In *Future Neurology*, Dr Tapuwa Musuka and I wrote a perspective article about the management of intracerebral hemorrhage (ICH) in 2020 [6]. The article discussed proposed methods of treatment. It must be understood that ICH is a huge challenge and, at the moment, current treatments are very marginal in their efficacy. Approximately 3 months ago, the biggest study ever completed on ICH was published [7]. The INTERACT2 study addressed the important question of whether early and intensive lowering of high blood pressure after an ICH could improve the chances of a patient surviving, free of major disability [7]. This study showed that there was a modest, but promising effect. Other strategies to treat ICH include prothrombotic medication and there are others who are looking at surgical options. My belief is that it is imperative to look at different medical approaches if you want to make a substantial impact. One of the things covered in our article was the idea of microvascular occlusion using catheters in the hope of identifying the bleeding source very accurately with the catheter and then actually subjecting the bleeding vessel itself. There is a group called PULSE Therapeutics (MO, USA), who are looking at magnetically labeled micro-particles that are injected into the circulation. At the moment, there is a very small pilot study small pilot study involving my colleagues Chris Levi (Hunter Health, New South Wales, Australia) and Chris Bladin (Box Hill Hospital, Victoria, Australia) that is looking at techniques where a patient admitted with stroke has intravenous iron filing particles injected into their

blood stream and, consequently, the individual has their head placed into a weak magnet, which then allows the small particles to be sucked into the clot interface [102]. This then permits thrombolytic therapy to be administered effectively. One problem with ischemic stroke is that there is stasis and lack of blood flow at the area of the clot. Therefore, if you think about the method discussed above, it would be interesting to observe this given to patients suffering from ICH. It could potentially allow prothrombotic drugs to be applied, enabling blood to be focally sealed off at the area of the hemorrhage. I believe that we should be thinking of novel therapeutics such as that.

Another aspect that we should be looking at is how we have become more advanced with our vascular imaging techniques. Approximately 3 years ago, there were detailed images of microscopic (50–100 μm) blood vessels rupturing, published in *Neurology* [8]. For the first time, we could actually visualize very small blood vessels that had burst owing to ICH. Using advances in vascular imaging, we could potentially combine an external beam or focus pulses such as radio-waves or heat using some type of stereotactic frame, which could potentially be used to cauterize the bleeding vessel quickly. I believe that the future of ICH treatment is looking at these more mechanical techniques that directly seal over the bleeding blood vessel. However, this is all very futuristic. Apart from the use of magnetic iron filings, the other techniques are not in practice at the moment.

■ **Is there evidence (from animal models) to suggest that combinatorial treatment may be effective in ischemic stroke? What are the future clinical prospects?**

The combination of tPA and minocycline has been demonstrated in a number of different rat experiments in the last 5–6 years. Recently, a group from the USA published their findings in experimental stroke [4]. It was observed that rats treated with tPA and minocycline demonstrated reductions in edema, inflammation and hemorrhage. We can see that this mode of treatment has a good basis in experimental animal models, and we are trying to jump straight into humans using this paradigm. In fact, one of my own colleagues (Bruno Meloni, The Australian Neuromuscular Research Institute, Perth, Australia) leads a experimental stroke laboratory that is currently studying modes of treatment that have been trialed in humans, such as magnesium and hypothermia in various combinations. I believe

there are groups in Canada that have studied four to five different methods of treatment, including hypothermia, magnesium, minocycline and a couple of other neuroprotective agents. Therefore, there is interest around the world. A group in Texas (USA) have looked at alcohol and caffeine together in rat models and are trying to translate this method into human beings. All these are interesting combinations that we hope will have theoretical benefits. There has been a lot of moves in the stroke world trying to standardize rat or other animal experimental models, making them a more realistic comparison with humans; however, the leap from rat to human has been difficult.

■ **How successfully are advances in basic science being translated into clinical care for stroke patients?**

A large number of neuroprotective agents for stroke looked promising in animal studies, but have failed to be translated into successful human clinical trials, for example, a number of neuroprotective agents that looked promising in rat models, failed when subjected to trials in humans. A few years ago there was a collaboration called stroke therapy academic industry roundtable (STAIR); the groups really strove to make rat models at least theoretically applicable to human models. In short, the answer to your question about the transition of basic science into clinical care, is that we have not been very good at all! However, restructuring trial design in a more rigorous fashion is now essential in stroke research.

■ **What are your roles & responsibilities in the stroke committees you are a part of?**

At the moment, I am involved in a number of committees. I am the chairman of the Scientific Organising Committee to the Stroke Society of Australasia's meeting, which was held from 31 July 2013 to 2 August 2013, in Darwin (Australia). The meeting combines Australia and New Zealand and we often get some Asian attendees as well. I am also on the committee for Australasia Strokes Trial Network (Melbourne, Australia). Therefore, while Australia is geographically big, the population is small so our stroke community is very tight knit. The Stroke Trials Network is a group represented from each state and we look at new trials from pharmaceutical companies and academic centers and try to see if they will be applicable to our local centers. Hankey and I have recently formed another group called the West Australian Stroke

Research Collaboration. At the moment, we have approximately 25 active members, ranging from basic scientists to epidemiologists and clinical trial and rehabilitation specialists. Therefore, we are just starting to get a little bit of momentum in stroke research in Western Australia; it is one of my keen interests at the moment in terms of research committees.

In terms of responsibilities, I am mainly a clinician, and I probably spend 70% of my time in the hospital or clinic, 20% carrying out research and 10% of my time teaching. My job as a neurologist consists of 50% stroke work and 50% general neurology.

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

As a clinician, I always think my greatest achievement is when patients are recovering well. In addition, it is always rewarding to get a paper published in an established journal. When I was at the Mayo Clinic from 2000 to 2003, I worked with a neurointensive care specialist called Eelco Wijdicks who ran the neurocritical care unit at Mayo. He has also been the chief editor of *Neurocritical Care Journal*. He is a very enthusiastic publisher; he sees every single bit of clinical information on the wards or in the intensive care unit as an opportunity to learn and publish. He really motivated me to publish. We brought together a small series of patients who had a massive hemispheric stroke and had developed an unusual sign, which meant that they suffered from ptosis, droopiness of the eyelids, and we wondered what this observation meant. We analyzed it quite carefully in six patients. These patients had massive strokes and there was a 50% mortality rate. We were able to carry out serial CT scans with them and study what was actually happening at the top end of the brainstem very carefully. From our observations, we noted that delayed bilateral ptosis occurred approximately 6–12 h before overt signs of cerebral herniation, and we thus considered this a 'warning sign'. There was some conjecture as to what causes this so we were ultimately successful in our argument to prove that. We eventually published this in the *Mayo Clinic Proceedings* [9]. I felt really happy when our reasoning was finally recognized and we got this into print.

■ **What is the greatest advance that you have witnessed during your time in the field?**

I think the attitude to acute stroke is the greatest change I have witnessed. I remember as an

intern when patients came into the emergency room with a stroke, there was this overwhelming sense that nothing could be done, which was also around the same time that coronary thrombolysis was being introduced. Patients with chest pain would be quickly assessed within 5 min of coming in with urgent ECGs, chest x-rays and blood tests, in the hope of providing these cardiac patients with thrombolytic therapy. By contrast, a neurology patient with a big stroke frankly looked a lot sicker than many of those cardiac patients and they were receiving no treatment. If we fast forward 20 years ahead, stroke is in that same exciting era. In Germany, there are stroke ambulances in which a CT scan can be carried out on the way to the hospital. An American group has just finished a study on intravenous magnesium given to patients in the back of the ambulance. Approximately 1400 patients were studied, with the vast bulk essentially being treated in the first hour or so. The recognition of stroke as an emergency, as well as the organizational and attitudinal changes in terms of our assessment, have been the most significant advances. However, we do need to provide better treatments for our patients.

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

I am currently working on a project that involves stroke rehabilitation. There is a curious phenomenon seen in stroke patients with paralyzed limbs, where the weak arm often moves impressively when the patient yawns [10]. This movement has been recognized for up to 100 years in the literature. It has been regarded as not meaning much, but I personally find it fascinating and we have been trying to put together observational studies to understand what it means. Could this observation mean that the patient is going to get better in the long run? Ultimately, I have planned a series of small projects put together in an attempt to figure out a little more about the phenomena, but ultimately it may be something that could be a trigger for a rehabilitation therapy. There is a very well-recognized phenomena of contagious yawning, for example, you are sitting in a room and someone yawns, then someone else yawns and it seems to spread like wildfire. It has been studied and it does not have any connection with oxygen or fatigue [11]. In fact, a feature of higher primate brains is that they recognize behavior in others. It has been observed that showing videos of chimps yawning to each other leads to a high percentage of them yawning [12]. What I postulate is that if we could

actually show a video of a patient yawning to themselves it may actually stimulate their arm to move. That could be the cornerstone of a therapy to get paralyzed limbs back into action, so that is what I am going to try and spend a bit of time studying over the next year or so.

■ **How do you foresee the field progressing in the next 5 years? What major challenges need to be faced?**

In terms of acute stroke, my hope is that there will be a lot more interest in the prehospital arena in terms of treatment and research. As I said before, German groups are looking at the stroke ambulance and American stroke specialists are starting a trial to study the prehospital field. There are a couple of people from the UK, for example, Professor Gary Ford at Newcastle University (Newcastle, UK); he is looking at a blood pressure study en route to hospital in the back of the ambulance. Most strokes cause damage very quickly in the first hour or so and, therefore, it seems logical that services are better organized and stroke is recognized as an emergency. I think it is very important that we start giving treatment extremely early. We have treatments that are marginally effective when they are started 3–4.5 h down the line. If we could move this forward to 1–1.5 h, our chances of making an improvement are probably much greater. I frankly think moving everything forward to the front of the hospital or even before the hospital should be the focus over the next few years. For many years, Geoff Donnan (The Florey Institute of Neuroscience, Victoria, Australia) and Steve Davis (Royal Melbourne Hospital, Victoria, Australia) have been advocating the use of advanced imaging in trials to select stroke patients that have tissue to salvage, beyond the traditional time windows. In fact, I am involved in one of their studies, which is selecting patients in the 4.5–9 h window, according to MRI criteria, where there still may be some benefits of thrombolytic therapy [13].

In terms of yield, I believe that looking at the hyperacute time window is probably where we will have a more significant effect, but there are many logistical and organizational challenges combined with that. One of the troublesome issues with stroke is consent to be enrolled into clinical trials, as patients cannot talk, understand or sign the consent forms. This is a challenge that everyone faces around the world. How do you randomize and consent these patients? There are some stroke therapies that clinicians are very convinced are effective but then find it

difficult to ethically give without seeking consent from their patients, who cannot give it. For example, a mode of therapy is mechanical clot extraction. This method involves a catheter, which passes a drip into the clot. There is also a mechanical suction device, corkscrew device or snare, which actually pull the clot out. These approaches are highly effective at opening up blood vessels and it was thought they would be the way forward. Some big studies (IMS 3 and SYNTHESIS) published in February 2013, did not really show superiority of these techniques over standard therapies, such as intravenous tPA, even in combination [14,15]. There are many potential logistical reasons for these observations. In Australia and other places in the world, we find a patient coming in with a major arterial occlusion and we know from observational studies that the chances of being able to open up the vessels using intravenous techniques are not very positive. Whereas, we know that the chance of the mechanical techniques removing the clot are actually quite high. There are many people who have an ethical dilemma of not subjecting those patients to proper randomization. We debate all these issues in stroke *ad infinitum*, and we recognize this as a challenge. Stroke is a very difficult area to study, but there are a lot of exciting things happening and I am optimistic that in the next 20 years there will be even better advances to come.

In terms of future challenges, we are faced with capturing the imagination of our younger doctors and getting them into the field of stroke. It is an exciting field, but we are struggling in Australia, at least in my area, to get some of our younger trainees interested in studying neurology in the first place. I personally believe that neurology continues to be viewed as a difficult, hard, academic specialty where you cannot receive high remuneration. I think younger

doctors see it as less well remunerated than other specialists, such as cardiology and gastroenterology. To some degree, the trainees may see it easier to do an endoscopy list and make a lot of money than to sit down and go through difficult diagnostic challenges, which are encountered with neurology patients. These advances in neurology in the last 20 years have been tremendous, not just in the field of stroke. For example, we now have six to eight new treatments that we can offer to multiple sclerosis patients. There are deep brain stimulation procedures for Parkinson's disease and other conditions, and there are even medical therapies, (admittedly of modest effect), for Alzheimer's disease. So diseases that had absolutely no therapeutic interventions, when I had first started practicing, now have promising therapies. I also think that MRI and functional imaging are just tremendous now.

Disclaimer

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

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