Stroke prevention - the simple truth

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From tracing missing patients to raiding dusty basements, Peter Rothwell has been finding new approaches to preventing stroke and cancer in some surprising places. He tells Lydia Harriss how the search for answers doesn't have to be complicated.

"I have written lots of rants in various journals over the years," says Peter Rothwell, Professor of Clinical Neurology and Director of the Stroke Prevention Research Unit at the University of Oxford, with a hint of amusement. It's hard to imagine the softly spoken Peter, sitting in his office with its tranquil views over leafy Oxfordshire, raging against the medical establishment. "You just wouldn't believe how much ridiculously simple clinical research hasn't been done that should have been addressed 50 years ago."

Peter's own knack for asking what he describes as "simple clinical questions" has led to an impressive array of discoveries that have challenged established medical understanding and helped transform clinical practice. His primary focus over the past 20 years has been to understand what causes stroke and what can prevent it, particularly in patients who have already had a minor stroke or transient ischaemic attack (TIA).

Stroke is estimated to be responsible for around 10 per cent of deaths worldwide and is caused either by blockage of a blood vessel supplying blood to the brain or by bleeding inside the brain. "From the patient's point of view, it causes a sudden-onset loss of some neurological function. It might be a sudden weakness down one side of the body or

loss of speech or vision," Peter explains.

In the UK, 150 000 people are estimated to have a stroke each year. According to Peter, roughly a third of these have major strokes that are "relatively disabling and require hospital admission". The other two-thirds have less severe and more transient symptoms, caused by strokes that fall into two categories: TIAs that last for under 24 hours and minor strokes that last from 24 hours up to several days.

Working at the John Radcliffe Hospital in Oxford in the late 1990s, Peter was treating patients who had experienced transient stroke-like symptoms and had been referred by their GPs for further investigation. Unsurprisingly, there were always some patients who did not turn up for their appointments.

Had they forgotten? Did they have more urgent things to do? No. When Peter and his colleagues conducted an audit to answer the seemingly trivial question - what happened to the missing patients? - they found that nearly every one had been admitted to hospital having had a major stroke.

Warning signs

"Until then, minor strokes and TIAs were thought to be relatively benign," Peter says. Previous research had shown that following a 'warning' TIA or minor stroke, "the risk of a major stroke was only about 1-2 per cent at one month and 2-4 per cent at one year". However, patients were only studied when they came to hospital for their appointments, which, Peter says, were often two to three weeks or sometimes months after the initial minor stroke or TIA. Consequently, clinicians and researchers had missed the short-term risk of major stroke during the first few days following a warning event.

Peter started a collaboration with local GPs. "We wanted to define the natural history [progression] of minor stroke and TIA properly, by studying patients from the onset of the event," he says. With a Senior Clinical Fellowship from the Medical Research Council, he established the Stroke Prevention Research Unit at the John Radcliffe Hospital in 2000 and the Oxford Vascular Study (OXVASC) in 2002. OXVASC has given Peter and his team access to almost all patients with minor strokes, TIAs and other acute vascular events within a population of 100 000.

Even Peter was surprised by what they found. "We worked out that the risk of [recurrent] stroke in the first week after a 'warning' event was about 10 per cent," he says [1]. As this was significantly higher than previously thought, he felt it called for a dramatic change in the way that the medical establishment and patients viewed TIA and minor stroke: "We wrote dozens of papers, boring our colleagues senseless, trying to rebrand this condition as an emergency."

Although OXVASC had made the case for treating minor stroke and TIA as emergencies, changes to medical guidelines and healthcare systems required more evidence. "We knew that antiplatelet drugs and blood-pressure-lowering drugs [common treatments for stroke] reduced the long-term risk of stroke, but there was no evidence that starting them immediately made much difference compared to starting them a week or two later," Peter explains.

Reducing the wait

His solution was to use OXVASC to study the effect of reducing the time that patients waited for treatment. OXVASC had already been seeing patients urgently in a daily clinic for two-and-a-half years, but had only been advising GPs on what treatments to prescribe. Peter and his colleagues made two simple changes. First of all, instead of using appointments, the clinic operated a 'walk-in' service that allowed patients

to be assessed more quickly. Second, treatments were started in the clinic rather than after a return visit to the GP (see 'Treating minor strokes', below). He and his team compared the risk of recurrent stroke in patients seen before the changes and patients seen after.

The results were striking. "We found that there was an 80 per cent reduction in the risk of early recurrent stroke," he says [2]. Such a marked improvement was difficult to dispute, and Peter's tenacity was finally rewarded when medical guidelines in the UK and internationally were changed to recognise minor stroke and TIA as urgent conditions requiring immediate treatment. Almost all hospital trusts in England now offer specialist clinics for the rapid assessment and treatment of these conditions.

"Stroke is one of the most common diseases in the developed world, yet we didn't even understand its natural history. I think that the public - and even non-clinical research colleagues - would be surprised about how much simple clinical research is yet to be done." It's an issue that Peter says extends beyond stroke. "For example, blood pressure is probably the most important single modifiable risk factor for disabling disease in the world, possibly apart from smoking. It causes dementia, heart attacks, stroke, all sorts of things, and yet we really don't understand it very well."

Rising pressure

"The clinical guidelines advised that doctors should measure the 'usual blood pressure'," a theoretical baseline, by taking blood pressure measurements many times over weeks and calculating an average. However, a patient's blood pressure often varies so much from one day to the next that, Peter says, the average level is not particularly informative. "Consequently, many GPs often found it difficult to apply the guidelines. They tended to believe the lower values, thinking that

these probably represented the underlying 'usual' blood pressure, and ignored the peaks."

Determined to explore this variation, Peter himself wore a blood pressure monitor 24 hours a day for six months. It made a whirring noise every 15 minutes as the cuff around his arm inflated to make a measurement. "It annoyed my wife intensely," he laughs, but "it did reassure me that this variability business was real. Until then, many people regarded variability of blood pressure as meaningless background noise."

It also revealed how strongly his own blood pressure depended on the activities he was doing. "Certain colleagues put my blood pressure up, other colleagues lowered it." In a single day at the 2008 World Stroke Conference, his blood pressure soared when he chaired a difficult meeting, dropped again afterwards, then cycled through a series of peaks and troughs as he gave a series of lectures.

By analysing existing data from several large studies of patients previously treated for TIA or high blood pressure, the Oxford team has highlighted flaws in the 'usual blood pressure' hypothesis [3] and shown that measurements of variability of blood pressure over time (such as the standard deviation) are more strongly related to a patient's risk of stroke than their average blood pressure level [4].

They have also found that some drugs being used to reduce average blood pressure, such as beta-blockers, increase blood pressure variability [5] and actually increase the risk of stroke. Others, such as calcium-channel blockers and diuretics, reduce variability and are particularly effective at preventing stroke. Peter says, "It's another example of simple clinical research that could have been done a long time ago."

Peter's talent for seeing new potential in old data has opened up another

avenue for his research. Driven by an interest in aspirin that stems from the Oxford TIA and minor stroke clinics' prescribing it to some 2000 patients every year, he has begun to look more closely at how it influences diseases other than stroke and heart attack. "Aspirin affects the main pathway that's responsible for inflammation and other fundamental processes in disease," he says. "It's inconceivable that it would only affect the risk of vascular events [such as heart attacks and strokes]."

He has spent months in dusty basements trawling through boxes of yellowing papers, hunting down data from old clinical trials involving aspirin. Using cancer registrations and other documents to track patients' health after these trials finished, he has found that a daily dose of aspirin substantially reduced the risk of patients' developing colorectal, oesophageal and other cancers for several years after the trials ended [6].

These findings have exciting implications for preventing cancer, which Peter and his team are continuing to explore. One of his most recent studies [7] indicates that aspirin can also prevent metastasis, the spread of cancer to other parts of the body. "I hope that will end up being a big new avenue for improving cancer survival rates," he says.

Research conducted in the 1960s showed that aspirin reduced cancer metastasis in mice [8] but wasn't investigated further at the time. "It's a good illustration of how there is sometimes a lack of joined-up thinking from the basic lab work to the clinical work. People don't always ask: 'How could we answer that question with existing data?'" Although Peter's tone is matter-of-fact, it's clear that he finds it frustrating.

Making more of the data and treatments already available is a theme that continues to run throughout Peter's research. With support from a Wellcome Trust Senior Investigator Award, he's developing techniques to predict the longer-term risk of recurrent stroke more accurately and

looking at whether blood pressure variability has a causal role in the development of other diseases, such as dementia. Aspirin also remains an important part of his work and he's continuing to explore the risks and benefits associated with it.

"Obviously we need to do basic laboratory-based research to develop new diagnostic tests and treatments...but we also need to put more effort into trying to do better with the tools that we already have," Peter says. His own work is a compelling example of what this can achieve. If his "rants" don't persuade his colleagues, perhaps his results will.

More information: References

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Treating minor strokes

Patients who have had minor strokes or transient ischaemic attacks can attend walk-in clinics at the Stroke Prevention Research Unit, University of Oxford. The process is:

- All initial investigations conducted on the same day - typically including magnetic resonance brain and arterial imaging and ultrasound imaging to measure blood flow, electrocardiography to detect heartbeat irregularities, and blood pressure monitoring.
- Treatment started immediately and patient sent home.
- Patient usually wears a heart rate monitor for five days to detect transient irregularities in heart rate and rhythm.
- Patient manually takes three sets of blood pressure measurements every day for at least a month. Results are automatically transmitted to the SPRU.
- Clinicians monitor blood pressure readings daily and modify treatment accordingly.

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