Can neurologists influence stroke incidence, and do they?

Sir William Osler could hardly have avoided writing about cerebrovascular disease. Although he attributed what we now call transient ischaemic attacks (TIAs) to the then fashionable notion of vasospasm, he did recognise them as episodes of transient cerebral ischaemia at a time when there were very few earlier or even contemporary descriptions. In the first edition of his textbook in 1892, he wrote: 'Transient hemiplegia, monoplegia or aphasia may occur in advanced arteriosclerosis', adding in the last edition that he authored, published in 1916: 'The attacks are very brief, lasting 24 hours or less'. Osler did not, however, appreciate that TIA patients were at risk of stroke – nor did anyone else at the time – but he was aware that they often experienced further episodes of hemiplegia and other signs of impaired cerebral function: '...recurrence is the rule, and a patient may have a score or more attacks of aphasia, or in the course of a couple of years there may be a dozen transient hemiplegic attacks or one or two monoplegias, or paraplegia for a day or two'. Certainly, Osler could have had no clear idea of what would reduce the risk of stroke after TIA; this knowledge has only emerged in the last 30 years as a result of randomised controlled trials (RCTs), and has been strengthened over the past ten years by the statistical technique of meta-analysis.

Diagnosis of transient ischaemic attacks

We now define a TIA as 'an episode of acute loss of focal cerebral or monocular function with symptoms lasting less than 24 hours, which is thought to be due to inadequate cerebral or ocular blood supply as a result of arterial thrombosis or embolism associated with arterial, cardiac or haematological disease'. In 1911 Osler wrote of TIAs: 'The diagnosis, usually easy, is based on the existing conditions of high tension or sclerosis or both, the slight and transient characteristic of the attacks, and the recurrences'. I agree that it is usually easy and one does not have to be a neurologist to diagnose most TIAs. However, it does help to be neurologically competent with easy access to neuroradiological expertise, because almost every condition that masquerades as a TIA is in some sense 'neurological'. For example, in the Oxfordshire Community Stroke Project, 50 GPs were asked to report those patients who they thought might have had a TIA. When examined by neurologists, almost two-thirds of these patients were found to have had something other than a TIA, the diagnoses ranging from syncope through migraine to cervical spondylotic myelopathy and a couple of meningiomas. In a world of ever increasing specialisation, then, it seems reasonable that these patients be seen by neurologically competent physicians, particularly when other specialists are becoming less willing or able to cope with 'neurology'. But maybe it was ever thus: Osler mentions a TIA patient who 'consulted a well known heart specialist, who said that he had chronic meningitis, gave him bromides, and his friends a hopeless prognosis'.

The prognosis for patients with TIAs

The diagnosis needs to be made quickly because some patients with non-TIA diagnoses need rapid treatment (eg for chronic subdural haematoma or heart block), the risk of stroke after a TIA is highest in the first few days and weeks, and most patients have been given a quite serious fright and are naturally concerned that any further attack could be much worse. The absolute risk of stroke after a TIA depends crucially on case mix, and it is, therefore, impossible to provide more than a rough estimate: about 4% in the first month, a total of 9% in the first six months and 12% by 12 months, and then about 4% per annum. Most of the strokes are ischaemic, usually in the same vascular distribution as the preceding TIA. In about 50% of TIAs, this is probably due to emboli shearing off a ruptured atheromatous plaque and obstructing smaller vessels downstream, at least until the plaque stabilises in some way (Fig 1). The rest of the strokes are mostly due to intracranial small vessel disease or embolism from the heart. Atherothromboembolism is an acute-on-chronic disease. Furthermore, it is a generalised disease; symptomatic disease in one place is commonly associated with either symptomatic or asymptomatic vascular disease affecting other organs. So, not surprisingly, TIA patients are at risk of myocardial infarction and sudden presumed coronary death, about 4% per annum; indeed, their most common cause of death is cardiac disease.

TIA patients are elderly and elderly people often have strokes. Are they at any greater risk than people of the same age who have not had a TIA? The answer is yes, about seven times.

Early attempts at treatment

Once the risk of stroke was appreciated, TIA patients were subjected to the rigours of treatment, starting with anticoagulants and carotid endarterectomy in the 1950s, but before there was any convincing proof that the theoretical
benefits outweighed the evident hazards. But to be fair, the serious evaluation of treatment with RCTs was then a very recent innovation – in the cerebrovascular field, Bill Fields in the USA and later Henry Barnett in Canada led the neurological and surgical communities into the era of RCTs, revolutionising the treatment of TIA patients.

**Carotid surgery**

The first randomised trial of carotid endarterectomy, the Joint Study of Extracranial Arterial Occlusion, led by Bill Fields, took place in the USA in the 1960s. It was, however, too small to be conclusive. Thus, whilst the surgical epidemic continued to flourish, neurologists remained sceptical at best and antagonistic at worst, an inevitable consequence of having a treatment that made theoretical sense – removing the stenosing atherothrombotic plaque at the origin of the internal carotid artery in the neck – but which was not supported by a convincing trial. The debate continued into the 1980s, spurring two large trials of carotid endarterectomy: one in Europe, completed in 1996, and the other in North America, completed this year. Both showed that, despite the peri-operative risk of stroke, patients with recently symptomatic and severe stenosis at the carotid bifurcation experienced overall long-term benefit because the much higher risk of untreated ipsilateral ischaemic stroke was almost completely abolished by surgery. However, if left untreated, the risk of stroke in patients with mild or moderate stenosis was so low that the risk of surgery was just not worth taking.

However, not all patients with severe symptomatic stenosis will have a stroke, probably only two out of ten, so that operating on all of them is, in a sense, unnecessary and sometimes damaging. Assuming that the risk of surgery, and the preceding angiography that is still usually required, is 10% stroke and death; that without surgery the risk of ipsilateral ischaemic stroke is 20% in two years; and that surgery abolishes all such strokes; then operating on 10 patients will cause one stroke and prevent two, a net benefit of one patient avoiding a stroke. There are two complementary approaches to reducing this 'number needed to treat': 1) make the treatment safer; and 2) offer it to patients who are at higher risk of what it can prevent, namely ipsilateral ischaemic stroke.

The overall risk of treatment would be reduced if intra-arterial catheter angiography were abandoned but it is not certain that the non-invasive alternatives of ultrasound, spiral CT and MR angiography are sufficiently accurate to select patients for surgery. Of course, surgeons are constantly attempting to improve the safety of their surgery but there is still uncertainty about many technical innovations because any RCTs have to be dauntingly large to demonstrate improvement on the already low surgical risk.

But what if patients could be selected who without surgery are at double the average risk of stroke, say 40% rather than 20%? Then, still with a 10% treatment risk, only about three would be operated on to prevent one having a stroke. Although the 'break even' point in favour of surgery seems to be at about 80% stenosis (Fig 2), only about two out of ten of these patients with severe stenosis go on to have a stroke, and so there must be other predictors, perhaps ulceration of the atheromatous plaque, or the frequency and site of the TIA. Although mathematical models to predict stroke can be constructed using these baseline data, they are not as accurate for individuals as for groups of individuals and have to be tested on another group of similar patients. So any prediction model derived from the European trial will have to wait for the completion of the North American trial, and vice versa.

The trials of carotid endarterectomy have shown that randomised comparisons of a surgical technique against no surgery are both feasible and believable, even when the technique is in common use; that physicians and surgeons can work productively together; and that European collaboration is neither a dream nor a nightmare, but a reality. However, it is unfortunate that the trials took so long. This problem of trial duration could be attenuated by a greater commitment to randomised trials by physicians and surgeons, and by provider units, and by a much harder push by health care purchasers to insist that medical interventions are properly evaluated.

**Antithrombotic drugs**

Despite its effectiveness, carotid surgery is applicable to fewer than 10% of TIA patients because about 35% are over the age of 75 and probably unfit for surgery, about 20% have ischaemic episodes in the vertebrobasilar rather than in the carotid circulation, and about 80% have either less than severe carotid stenosis or inoperable carotid occlusion. Are there any medical treatments that might benefit the other 90%, and indeed the surgical patients who remain at risk of ischaemic strokes outside the operated vascular territory, and of coronary vascular events?
Oral anticoagulants were introduced into medical practice in the 1940s, and not surprisingly, were soon being used in TIA patients. However, this treatment was never properly evaluated and had fallen into disrepute by the 1960s, at least for patients with no obvious source of embolism in the heart. Furthermore, because platelets are a more prominent component of arterial than of venous thrombi, antiplatelet drugs came into clinical use.

The antihaemostatic properties of aspirin had been known for decades and in the 1950s Lawrence Craven, a general practitioner in Glendale, California, suggested that this very property might mean that it would prevent strokes and heart attacks. Maybe someone would have noticed this suggestion sooner if he had published his thoughts in something with a higher impact factor than the now defunct *Mississippi Valley Medical Journal*. In the event, the antiplatelet properties of aspirin were not described until the late 1960s and by then RCTs were *de rigueur*.

The first large trial of aspirin for TIA patients was started in Canada in 1971 by Henry Barnett, along with the then almost unknown methodology group at the new MacMaster Medical School, in particular Mike Gent and Dave Sackett. Although the trial did seem to show some benefit from aspirin, it was criticised for what has now turned out to be an inappropriate subgroup analysis that suggested that aspirin worked in men but not in women. As a result of this promising, but not completely convincing result, about a third of all the neurologists in the UK set up the UK-TIA Aspirin Trial which compared a lower daily dose of aspirin of 300 mg with the Canadian high dose of 1,300 mg and with placebo. But even with over 2,000 patients, the trial yielded a non-significant 15% odds reduction in serious vascular events.

By the late 1980s the results of a bewildering number of trials had become available, testing not just aspirin in various doses but also other antiplatelet drugs, and in a wide range of ‘vascular’ patients such as survivors of myocardial infarction, claudicants and diabetics. Fortunately, to make sense of the apparently conflicting results of several trials of similar treatments for similar patients, the statistical technique of meta-analysis was being developed through the late 1970s and in the 1980s, particularly by Tom Chalmers in Boston and Richard Peto and Iain Chalmers, both in Oxford. Richard Peto was closely involved with the UK-TIA Aspirin Trial, and so it was quite logical for him to pull together all the main players in the other antiplatelet drug trials to form the Antiplatelet Trialists’ Collaboration (APT), recently renamed the Antithrombotic Trialists’ Collaboration (ATT), now that other antithrombotic drugs, such as warfarin, have been included. The group published their results first in 1988, updated them in 1994 and the latest results were presented in Oxford in September 1997.

The message in 1994 was quite simple: no antiplatelet drug was more effective than aspirin which has the advantage of wide availability, familiarity, low cost and reasonably few adverse effects; 75 to 325 mg per day was the appropriate dose although there is now evidence that as little as 30 mg per day may be sufficient. The group also concluded that there was no discernible difference in the 25% relative odds reduction of serious vascular events likely to be influenced by antiplatelet drugs in different categories of patients (TIAs, claudicants, angina and so on) of both sexes, at various ages and whether hypertensive or diabetic.

We now have the possibility that other antiplatelet regimens are better than aspirin alone. Ticlopidine was already looking promising in the 1994 APT meta-analysis, and with the CAPRIE trial of clopidogrel, it seems that thienopyridines are a little better than aspirin. The situation with dipyridamole is more confused. So far, it provisionally...
looks as though the combination of dipyridamole with aspirin, compared with aspirin alone, may reduce the risk of stroke, but not the risk of coronary events, in high vascular risk patients.

What does all this mean for TIA patients, and for the qualitatively similar mild ischaemic stroke patients? Aspirin will reduce their risk of stroke, myocardial infarction or vascular death from about 12% in two years to about 9%; in other words, 100 patients have to be treated for two years to prevent three of them having a serious vascular event or, putting this another way, one has to treat about 33 patients for two years to prevent one having a serious vascular event. Because aspirin is so cheap, this is a very cost-effective treatment but it does mean that a lot of TIA patients have to take aspirin without any benefit to themselves, perhaps of little consequence when considering aspirin rather than much more costly and risky treatments. Some prognostic models have been developed to pick out particularly high risk TIA patients; but to treat only this group with aspirin would leave most patients untreated, yet it is from the latter that the majority of strokes emerge (Table 1). This is a familiar paradox in preventive medicine; most cases of anything arise not amongst the small number of people at highest risk because there are not very many of them, but amongst those at moderate risk because their numbers are far greater. So, for the time being, it makes sense to give aspirin to all TIA patients, provided they can tolerate it – which most do, particularly if it is enteric coated.

Meanwhile, other treatments have been explored. The uncertainty surrounding TIA patients with non-rheumatic atrial fibrillation was resolved by the European Atrial Fibrillation Trial which showed that anticoagulation with a target INR of 3.0 reduced the risk of stroke by about two-thirds without a major problem with bleeding, and that it was better than aspirin24. However, it will be a considerable challenge to any health care system to deliver anticoagulation safely, even to patients with no obvious contraindications. Also, whilst at long last anticoagulation is being properly tested in TIA patients in sinus rhythm, so far it seems that the risk of bleeding is unacceptably high in comparison with aspirin25.

Reversing vascular risk factors

Reversing causative vascular risk factors in TIA patients makes sense but it is difficult to prove that it makes a difference. Of course, there are so many good reasons to stop smoking that proof in TIA patients is hardly required. For diabetes there is still no evidence that the macrovascular complications, such as stroke, are prevented by better glycaemic control but symptomatic diabetes obviously needs treatment in its own right. A raised plasma cholesterol level is a strong risk factor for coronary events but curiously not for stroke26. Nonetheless, stroke risk may well be reduced by lowering cholesterol with statins, at least in coronary and asymptomatic patients27. We still need to know for sure whether statins reduce stroke risk in TIA patients, although, presumably, they reduce their risk of coronary events. But what about the most important stroke risk factor of all, high blood pressure? Not only is there a strong relationship between usual blood pressure and first stroke, but the relationship is just as strong for stroke occurring after patients have presented with a TIA or minor stroke (Fig 3). How much the blood pressure should be lowered and whether the likely benefit will be attenuated by precipitating cerebral ischaemia in TIA patients, who might have reduced cerebral perfusion reserve and impaired autoregulation, is not clear and a large international trial is addressing this issue28. One can hope Osler will be proved wrong here because he attempted to lower the blood pressure just to relieve symptoms ‘rather than with any hope of essentially influencing the disease’.

Reducing the incidence of strokes by treating TIA patients

TIA patients can now be identified from among the mass of patients with other ‘funny turns’ and have their risk of serious vascular events reduced, perhaps even halved. This need not be done by neurologists but can be done by physicians with training in stroke medicine. We clearly can prevent strokes and presumably are preventing strokes. A lot of good is being done at the individual patient level. But what effect might all this have on the number of people who have a first stroke every year, and what effect is it actually having? The short answer to the first question is, not a lot, and to the second is, that we can’t tell.

Aspirin

Every year about 21,000 patients with TIAS come to medical attention in England and Wales29 and about half of them die within about 10 years30; so, very roughly, about 210,000 patients who have had a TIA are alive at any one time.

| Predicted risk (%) | No. of patients at risk | Patients having a stroke No. | Percentage of all patients who had a stroke (%) |
|--------------------|-------------------------|------------------------------|-----------------------------------------------|
| 0-10               | 604                     | 37                           | 6                                             | 21                                            |
| 11-20              | 671                     | 77                           | 11                                            | 43                                            |
| 21-30              | 228                     | 41                           | 18                                            | 23                                            |
| 31-40              | 75                      | 8                            | 11                                            | 4                                             |
| 41-50              | 33                      | 5                            | 15                                            | 3                                             |
| 51+                | 40                      | 11                           | 28                                            | 6                                             |
| **Total**          | **1,651**               | **179**                      | **11**                                        | **100**                                       |

Table 1. Number and percentage of strokes that occurred in 1,651 TIA patients in the UK-TIA Aspirin Trial, divided by predicted baseline risk derived from an independent model. (Reproduced from reference 23 by permission of the BMJ Publishing Group.)
Given an annual stroke risk of maybe 6%, about 13,000 will have a stroke every year. If aspirin reduces this by 25%, then roughly 3,000 strokes will be prevented. Although this is an impressive number, implying that much misery and many resources will be saved, it is actually only about 3% of all the 100,000 patients a year who have a first ever in a lifetime stroke. Why such a disappointingly tiny proportion? The main reason is that only about 15% of strokes are preceded by TIAs, so even if all TIA patients could be recognised and treated completely successfully, overall stroke incidence could not possibly fall by more than 15%. Of course, we will never achieve that. Our best efforts are thwarted because perhaps 50% of TIA patients do not come to medical attention until after their stroke, and stroke can occur so quickly after a TIA that we do not have time to start treatment; treatment is not 100% effective anyway, and patients may not accept the treatment offered.

Carotid endarterectomy

Although carotid endarterectomy has a much greater treatment effect than aspirin, it is the appropriate treatment in such a small proportion of TIA patients that it can prevent only a minute proportion of all incident strokes (Table 2). Similar calculations show that even if all the prevalent fibrillating TIA patients were anticoagulated, which would be neither sensible nor practical, stroke incidence would fall by a trivial 2.5% (Table 3). Likewise, lowering the blood pressure of hypertensive TIA patients would reduce stroke incidence by only 2% if the treatment effect turns out to be as good as we hope (Table 4). However much good we do for the individual TIA patient, at the population level the effect is trivial, a general paradox emphasised by the late Geoffrey Rose in The strategy of preventive medicine. What is good for the individual is not necessarily equally good for society, a principle that resonates far beyond medicine. What we are doing with TIA patients is identifying and treating a group of people at particularly high risk of stroke, but we must remember that most strokes arise in the much greater number of people who have never had a TIA, in the same way that many more strokes arise in the much larger number of people who have moderately raised blood pressure than in the small number who are declared to have severe hypertension. From the population point of view there have to be additional and better ways of reducing stroke incidence as well as treating just those at highest risk of stroke, the so-called mass strategy which inevitably has to do with political action on diet, smoking and exercise. This is quite another issue, albeit a crucially important one.

Given the likelihood that treating TIA patients will have only a small effect on the incidence of stroke, it is inher-

Table 2. The estimated impact, in terms of strokes prevented and reduced stroke incidence, of treating recently symptomatic patients with severe carotid stenosis in England and Wales with carotid endarterectomy.

|                        | England                                    | Wales                                      |
|------------------------|--------------------------------------------|--------------------------------------------|
| Number of TIA patients | 21,000                                     | 30,000                                     |
| Number of minor ischaemic strokes | 33,150                                   | 5,304                                      |
| Total: 51,000          |                                            |                                            |

Approximately 65% under the age of 75: 26,520
About 80% have 'carotid territory' ischaemia: 5,304
About 20% have 80-99% carotid stenosis: 5,304
If operating on 9 patients avoids one stroke in two years, then operating on 5,304 patients will avoid 589 strokes in two years
This is well under 1% of all the 130,000 first ever in a lifetime and recurrent strokes that occur every year
ently unlikely that we will ever be able to detect the change. Measuring stroke incidence reliably just once is difficult enough, but then to keep going with the same rigorous methodology and monitor its incidence over years is so difficult that it has hardly ever been achieved\textsuperscript{14}. Furthermore, the sample sizes and the accuracy have not been sufficient to pick up a change in incidence of a few percentage points. Monitoring stroke mortality from death certificates is much easier and may even be good enough for the really major changes expected by the government in their \textit{Health of the nation}\textsuperscript{15} initiative. But were these large changes actually to occur, they could not possibly be explained on the basis of neurologists and others treating TIA patients.

\textbf{Evaluating the treatment options}

As new and more promising treatments are developed, it will be important to set up randomised trials and incorporate the results into continuously updated meta-analyses of the sort being conducted by the Cochrane Collaboration\textsuperscript{16}. This is a good point at which to acknowledge those who pay for all these efforts at evaluation, in particular the Medical Research Council which has such a long and honourable history developing and funding clinical trials; increasingly, the Departments of Health are not just encouraging but are now paying for treatment evaluation, and the Cochrane Collaboration would not have happened without their support. The pharmaceutical industry puts vast resources into clinical trials but often is so intimately involved in their design, execution, analysis and publication that a conflict of interest is suspected even if none exists. In any event, industrial money must not be allowed to distract us from promising surgical techniques, physiotherapy, psychology and other interventions that require just as rigorous evaluation as drugs, nor, indeed, from old non-patented drugs such as aspirin.

\textbf{Getting the message across to medical students}

Where can we best put across to medical students the public health messages outlined in this paper, as well as the traditional doctoring issues of diagnosing and treating TIA patients? My preference, as a clinician, is 'at the same time in the same place': in other words, at the bedside or, more often these days, in the outpatient clinic or general practitioner's surgery. Osler would have approved; during his valedictory address to Johns Hopkins University before leaving for Oxford, he said: 'I desire no other epitaph than that I taught medical students in the wards, as I regard this as by far the most useful and important work I have been called upon to do\textsuperscript{12}'.

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