Introduction to the ACNR Stroke Series

Stroke is the commonest neurological condition by some margin, and has been estimated to cause more than 50% of the burden of disease (in terms of quality adjusted life years) of all neurological conditions. It is the third commonest cause of death and leading cause of adult neurological disability. In the last 20 years, stroke has undergone perhaps the most dramatic increase in understanding and treatment (from hyperacute care through to prevention and rehabilitation) of any neurological disease, making it a very exciting time to work in the field.

The aim of this series for ACNR is to capture some of the excitement of recent advances (from endovascular therapy to stroke prevention and rehabilitation) with an eye to future developments including the increasingly important areas of stroke genetics, vascular cognitive impairment and cerebral haemorrhage. However, the series also touches on some of the historical foundations of modern stroke medicine. With the huge breadth of research related to stroke, this series can only hope to provide a highly selective glimpse into a few aspects. Nevertheless, we hope that it will be of interest to both experienced neuroscience clinicians but also to younger clinicians and researchers in the neurosciences; there has never been a more exciting time to start a career in stroke medicine or research.

In the first article in this series, Dafydd Thomas and colleagues provide a fascinating and inspiring account which reminds us of how many fundamental concepts (e.g. that of the ischaemic penumbra, which underpins thrombolysis and endovascular treatments) and technological developments (e.g. computed tomography and magnetic resonance imaging) owe much to the pioneering work done by British researchers, mainly in the latter part of the 20th century.

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Foundations of Modern Stroke Medicine: The British Contribution in the 20th Century

At the end of the 20th Century, not only were we much less likely to suffer a premature stroke than at the start of the Century, but also much more likely to receive an accurate diagnosis and effective treatment. This paper attempts to summarise some of the critical British contributions to the advances in stroke prevention and treatment, but does not pretend to be a comprehensive review.

From being a ‘Cinderella disease’ where it was felt that little could be done and patients were sometimes left ‘languishing’ in medical wards, often for months, our main hospitals now have urgent transient ischaemic attack (TIA) clinics, hyperacute stroke units (providing thrombolytic treatment), and active rehabilitation services.

Pathophysiology

A greater understanding of the control of the cerebral circulation in health and disease was achieved using newer techniques for measuring cerebral blood flow (CBF). Murray Harper’s work improved awareness of cerebral autoregulation, by which blood flow is kept constant, with changing blood pressures (see Figure 1, which shows a stable CBF throughout a wide BP range). At very high blood pressure, autoregulation begins to fail and CBF rises, increasing the risks of oedema and haemorrhage. The concept developed that blood vessels in the neighbourhood of a stroke were also damaged and lost the ability to autoregulate. Local CBF then became dependent on blood pressure (the pressure-passive response) and vulnerable to both low and high blood pressures.
The Queen Square CBF group (du Boulay, Marshall, Ross Russell and Symon) was set up following the innovative work of Lassen and Ingvar. The group helped emphasise the role of CO2 in controlling CBF and the influence of high blood viscosity and high haematocrit in lowering CBF. Venesection was shown to have a dramatic effect on increasing CBF even in people with haematocrit levels in the upper normal range. Substantial reductions in risk of occlusive vascular events, including stroke, in patients with polycythemia was achieved by advising the lowering of the target haematocrit from 0.50 to below 0.45, thereby halving the whole blood viscosity. However, enthusiasm for using haemodilution to improve CBF after stroke in patients without polycythemia waned in the UK, when the Queen Square CBF Group went on to show that CBF increased largely due to maintaining oxygen delivery rather than due to lowering viscosity. Nevertheless, haemodilution continued to be used for some years elsewhere in Europe and in the USA to increase CBF reasoning that increasing blood flow to vulnerable areas was beneficial however it was achieved.

The important concept of the ischaemic penumbra, with threatened but still viable cells surrounding a severely ischaemic centre and thresholds in cerebral ischaemia was investigated by Lindsay Symon's group at the Institute of Neurology, Queen Square. This concept underpins the only licensed treatment for acute ischaemic stroke: intravenous thrombolysis. Ischaemic areas lose autoregulation and perfusion can be increased by induced hypertension. The potential damaging effect of low blood pressure in the presence of cerebral vasospasm after subarachnoid haemorrhage and the benefits of improving blood flow and cerebral function by raising blood pressure were advocated by them. The syndrome of critical brain perfusion and the clinical recognition and treatment of borderzone (watershed) infarction of the brain was emphasised.

Pathophysiology

The importance of transient ischaemic attacks (TIAs) as warnings of impending strokes was highlighted by Acheson and Hutchinson's natural history paper; they emphasised that the vertebral arteries were also important and recommended that they should be routinely examined. Initially TIAs were thought to be due to 'vasospasm'. Sir George Pickering was one of the first to doubt this. Attention turned to a haemodynamic insufficiency with short-lived reductions in blood flow to a vulnerable region provoked by a fall in blood pressure. However, the work of Marshall and Kendall showed that lowering blood pressure led to global syncopal symptoms, rather than to the focal ones typical of TIAs.

After Miller Fisher's suggestion that embolii from thrombus in neck vessels might be important, came Ross Russell's observations of repeated emboli moving through the retinal arteries in patients with carotid stenosis. The view that most TIAs were thrombo-embolic in origin was strengthened. Attention then focused on potential sources of cerebral emboli not only from the aorta and other major vessels, especially the carotid bifurcation, but also from the heart. The importance of atrial fibrillation became clearer. The role of paradoxical emboli, especially through the commonly patent foramen ovale (PFO), generated much interest and discussion on the pros and cons of closing the PFO, and the role of transcranial Doppler techniques for detecting ongoing micro-emboli. The significance of platelets in the growth and embolisation of mural thrombus attracted much interest. The use of anti-platelet therapy in reducing thrombo-embolism was stimulated. Ross Russell's work on cerebral microaneurysms in the brains of patients with hypertension, and their potential role in cerebral haemorrhage, was a major contribution: renewed interest has been aroused by the demonstration of microbleeds on blood-sensitive MRI, some of which may be associated with microaneurysms.

Epidemiology

The incidence of stroke fell in developed countries from the mid 20th Century even before effective treatment became available. A similar decline in myocardial infarcts has also occurred. The reasons for this have not been fully explained. Less cigarette smoking has contributed. A controversial suggestion is that the increased availability of refrigeration, both commercially and domestically, substantially reduced the need for salt as a food preservative. This may have had an effect on reducing the prevalence of high blood pressure, the most important remediable risk factor for stroke. The role of infection in increasing the risks of thrombo-embolism, myocardial infarction and stroke and the widespread use of antibiotics possibly reducing these risks also need to be considered.

The Oxford Community Stroke Project was set up by Charles Warlow in the 1980s and it continues to provide useful information, e.g. the proportion of strokes due to cerebral haemorrhage has fallen substantially. There are, nevertheless, still approximately 150,000 new strokes in the UK each year. Stroke remains a major cause of death and the main cause of ongoing disability. Prevention remains a top priority.

Prevention

Since age is the main risk factor for stroke and since the effects of different risk factors are cumulative, it may be more important to treat the elderly than those in younger age groups. This was not appreciated until recently; up to the 1980s, high blood pressure was often left untreated.

Blood Pressure Treatment

Hypertension used to be considered to be a disease, not just as the upper end of the BP range. It is better regarded as a continuum. The BP level at which treatment is recommended has come down and continues to do so. There have been some excellent blood pressure randomised multicentre trials, including the huge ASCOT study coordinated by Peter Sever's team from St Mary's Hospital.

From advising 'just bring the blood pressure down', management has matured, with the demonstration that different hypotensive agents may have different benefits and disadvantages at different ages and in different racial groups. In patients following stroke, a raised blood pressure was previously often left untreated. Now there is a substantial body of evidence of benefit from lowering BP to prevent stroke.

Anticoagulant Treatment

Anticoagulant treatment was effective at preventing thromboses in several clinical situations. So, Marshall, Shaw and Bradford Hill performed a very early trial of anticoagulation in TIAs. The results were inconclusive, possibly as a result of small numbers, but also because the ethics of the time ruled that it was unacceptable for the control group to have a placebo. So their controls were given 1mg of warfarin/day, which was then thought to be ineffective. So it was really a trial of 'normal' warfarin doses, controlled by INR versus low dose warfarin; some of the control group might thus have had some anti-thrombotic protection.

Antiplatelet Treatment

The role of platelets in TIAs became a concern in the 1960s and 1970s. The UK-TIA Aspirin Trial, at the time the biggest study randomising 3,000 patients failed to show a statistically significant benefit on reducing the risk of stroke in patients presenting with TIAs. This was a stimulus for the introduction of meta-analyses of similar trials. Meta-analysis of the aspirin trials available did show a modest benefit in reducing the risk of stroke and myocardial infarction. Low dose aspirin seemed as effective as high dose and was somewhat less likely to produce side effects. Increased statistical awareness has improved trial design. The development of the Clinical Trials Service Unit in Oxford and the International Centre for Circulatory Health at St Mary's, among others, have allowed the UK to coordinate and to participate in several important vascular trials of other anti-platelet agents and fibrinolysis.

Other Preventative Measures

The use of statins has become widespread. Statins are now introduced at cholesterol levels which would have gone untreated in previous decades.

The harmful effects of poorly controlled blood glucose levels in diabetics are now
better appreciated, with concerns over the risks of larger strokes with higher glucose levels.\textsuperscript{21} Extensive studies of diabetes management have been carried out by UK clinicians, involved in the largest cohort studies in the world.

Bickerstaff's monograph\textsuperscript{26} on 'Neurological complications of oral contraceptives' highlighted the potential risks of stroke. The OCP formulations have since been improved and many strokes prevented.

The important work of Richard Doll and Richard Peto on the risks of smoking has done much to reduce the prevalence of smoking in Western Countries and to reduce substantially the risks not only of cancers but also of vascular disease and strokes.\textsuperscript{27}

**Carotid Artery Stenosis**

In 1954 a team from St Mary's first reported a carotid artery reconstruction in a successful attempt to prevent TIAs progressing to a stroke.\textsuperscript{28} This triggered a widespread enthusiasm for carotid endarterectomy. Physicians' concerns were raised about the number of strokes actually being caused by carotid endarterectomy and the invasive angiography that preceded it. So, in the early 1980's the European Carotid Surgery Trial\textsuperscript{29} was started, by Charles Warlow with the same core of collaborators as in the UK TIA Aspirin Trial. In 1991, they reported that in patients with more than 70\% stenosis, there was an impressive reduction in the risk of stroke. The results were confirmed by a North American Trial\textsuperscript{30} coordinated by British born neurologist, Henry Barnett. In addition to clear evidence of efficacy we now also have a better idea on patient selection.\textsuperscript{31}

These studies triggered two large trials of carotid endarterectomy in asymptomatic patients with tight carotid stenoses: the Stroke Association's and Medical Research Council's Asymptomatic Carotid Surgery Trial, ACST\textsuperscript{32} and the North American ACAS trials. These again showed a benefit with a 50\% reduction in the risk of stroke, but the absolute risks in asymptomatic patients are low and the peri-operative risks are not negligible. This has led to a strange polarisation of management advice: Patients seeing surgeons may be advised to have an endarterectomy because by doing so the risk of stroke is significantly reduced. Those seeing a physician may be advised that the absolute risk is low and that best medical treatment should suffice pending any TIAs. There has also been enthusiasm for using carotid angioplasty and stenting instead of endarterectomy. Questions remain. The trials continue. ACST2 and ECST2, both UK-led trials, are now recruiting.

**Rapid access TIA Clinics**

The realisation that the risks of stroke were highest soon after a TIA and that if surgery were delayed the benefit would be lost has led to a change of attitude and the establishment of urgent TIA clinics around the Country, based on evidence in part from the OXVASC study led by Peter Rothwell. The aim is to see patients and to investigate them promptly including with brain scanning and carotid imaging within 24 hours rather than being set-up just where local neurologists or physicians were interested, a TIA service became a priority for NHS managers.

**Acute Stroke Diagnosis**

Perhaps the greatest contribution to stroke diagnosis and management was the Nobel laureate Sir Godfrey Hounsfield's (see Figure 2), invention of computerised axial tomography.\textsuperscript{33} Before the CT scan it was difficult to know whether a stroke was due to an infarct or haemorrhage. Now it is possible to detect significant amounts of acute cerebral haemorrhage within minutes.

As well as permitting anatomical localisation, images of the major arteries are possible and thrombolytic treatment can be given promptly. Thrombolytic treatment had been tried in the late 60's and early 70's, but was abandoned because of fatal haemorrhages—usually in those patients whose stroke had in fact been a haemorrhage, but diagnosed as an infarct (Thomas DJ personal observations). See Figure 3 of a CT brain scan showing a recent cerebral haemorrhage, a clear contraindication to thrombolytic therapy.

Diagnosis was further improved by extending the X-ray computerised tomography techniques to nuclear magnetic resonance imaging, for which Sir Peter Mansfield (see Figure 4), also won a Nobel prize.\textsuperscript{34} 'Nuclear' was dropped to avoid confusion with ionising radiation. The development of different MR sequences including diffusion-weighted imaging and MR angiography have transformed our assessment and understanding of stroke and have helped improve management. See Figure 5, a diffusion weighted image (DWI) MRI scan showing a recent small subcortical cerebral infarct. An under-emphasised advantage of early brain imaging is that it prevents patients with non-stroke conditions, masquerading as a stroke ('mimics'), receiving inappropriate treatment.

**Acute Stroke Treatment**

**Stroke Units**

It came as a surprise that even before any apparently effective treatments became available, patients in units dedicated to stroke care did better than those on general wards.\textsuperscript{35} This was not an isolated finding. The reasons are not immediately apparent. Was it just the MDT approach with the concentration of interested medical, nursing and physical therapy staff? Certainly awareness of swallowing difficulties and improved care of the airway helped prevent aspiration problems and undernutrition and dehydration. Hospital trusts became really motivated to provide stroke units only after thrombolytic therapy was accepted to be effective and the number of acute units greatly increased. Many hospitals now have hyperacute units for the first few days with patients moving-on to stroke rehabilitation areas. Lengths of hospital stay have been reduced substantially, and outcomes seem to be improved. The Royal College of Physicians' national sentinel audit for stroke has raised standards and significantly improved stroke care.\textsuperscript{36} With a motivated, well-coordinated ambulance service and increased patient and relative awareness, some hospitals are now able to offer thrombolytic treatment to up to 30\% of their cases.

**Other Acute Treatments**

In contrast to the success of thrombolytic treatment,\textsuperscript{37} neuroprotective agents have been disappointing.\textsuperscript{38} Anticoagulants may have a role (as yet unproven) but only in carefully selected patients.\textsuperscript{39} Antiplatelet agents are role (as yet unproven) but only in carefully selected patients.\textsuperscript{39} Antiplatelet agents are worth introducing as a secondary prevention after acute stroke to reduce the risk of a recurrent stroke, but the number needed to treat is high.\textsuperscript{40} The need to control glucose levels may not be sufficiently addressed. The use of glucose, potassium and insulin infusions were tried again, after a 30 year interval.\textsuperscript{41}
Cerebral Haemorrhage

Most of what has been said so far has referred to cerebral infarction. Although some of the same risk factors are involved and rehabilitation may be similar, the acute management of cerebral haemorrhage is quite different. Sir Wylie McKee-Sock, the influential neurosurgeon at Atkinson Morley’s Hospital and Queen Square, tested the effect of removing intracranial haematomas in stroke patients. His results were somewhat discouraging.46 So surgery, with the exception of that for acute cerebellar haemorrhages was largely abandoned in the UK until David Mendelow and his colleagues re-addressed the question. With better modern anaesthetic and post-operative care and less invasive surgery, a multicentre trial was set-up (STICH). Again the results have been discouraging, failing to show overall benefit from surgical evacuation.47 However trials of acute blood pressure lowering in cerebral haemorrhage have been promising and a large UK-led trial of tranexamic acid is underway.

Subarachnoid Haemorrhage

There have been significant advances with fewer open operations, more endovascular procedures and better measures to recognise and control the effects of cerebal vasospasm and maintain cerebral blood flow. Calcium antagonists have been used.48 Treatment of hydrocephalus has been improved.49

Rehabilitation

Rehabilitation results are improved after good acute care, which has minimised the volume of brain damage and has prevented pressure sores, venous thromboses, shoulder subluxation and contractures which all make therapy more difficult.

Therapy can begin in the acute unit, particularly with correct positioning, swallowing assessments, protection of the airway and maintaining nutrition. A goal-orientated approach with a skilled MDT is now widely recommended. The days of not emphasising speech therapy because it was little better than ‘just talking to the patient’ and not offering a place in rehabilitation to those with marked inattention are happily past. Modern MRI with functional imaging may help with prognosis, predicting and planning brain recovery. The need to recognise those with dementia and other cognitive problems is now better understood, thus stimulating continued advances in this exciting field.

The Future

The Royal College of Physicians (36) has had an important role in improving stroke services around the UK; the college stroke audit highlighted deficiencies, and managers were motivated to rectify them. The monitoring looks likely to continue. There is no place for complacency. The Stroke Association’s survey of patients and carers found that a major criticism was that they felt abandoned on returning home from hospital. There was a sudden lack of medical and nursing care and a dramatic drop in therapy. This separation of hospital and community services needs to be addressed. This problem is not confined to the United Kingdom. In addition, it is disappointing that health and social services remain separated in the UK.

The NHS provides a unique opportunity for translational research, stimulating the creation of the National Institute for Health Research (NIHR) and Stroke Research Network, which has dramatically increased participation of stroke patients in research studies (from about 2,000 per year in 2005 to over 12,000 per year in 2012), which should continue to have farreaching beneficial effects.

In the UK, neurologists have been slower to take on the management of the hypertensive stroke units in the same way as their European and North American colleagues. Hopefully this will be rectified by improvements in the UK training programmes to allow stroke (and any other acute neurological conditions that can mimic it) to play the central role it deserves in the training of UK neurologists.
November
Improving Patient Pathways in Parkinson’s Disease meeting
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Supported by Genus Pharmaceuticals.
Register for free at www.parkinsons-ha.co.uk or www.apo-go.co.uk/hcp/events/PRM-2013

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9th ESSENTIAL NEURO MRI Course
Sat 19 Nov, 2011; Liverpool, UK
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December
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Free entry for our Professional Members, for more information:
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Multiple Sclerosis 2013
2 December, 2013; London, UK
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