Editorial

What has gone wrong in stroke research?

There have been two main approaches to the acute treatment of stroke, thrombolysis and neuroprotection. After a number of disappointing thrombolytic trials using either streptokinase or an inappropriately long time-window, tissue plasminogen activator (t-PA) was demonstrated to improve clinical outcome at three months. Patients who received t-PA within 3 hours of onset were 30% more likely to have minimal or no disability at 3 months when compared with placebo. This was at the price of 6.4% of patients, who received t-PA and developed symptomatic intracerebral haemorrhage, producing a non-statistical benefit in terms of mortality (17% vs 21%). For many patients, disability is a more important issue than death and t-PA reduces disability, but will cause some deaths from haemorrhage.

Normal cerebral blood flow is approximately 100 ml/100 g of brain tissue per minute. In cerebral infarction there is a core of tissue with blood flows in the 0–10 ml/100 g/min range where neuronal death will occur within an hour and the damage is irreversible. Around this is an area of brain called the penumbra, where blood flow is in the 10–20 ml/100 g/min range. In the penumbra there is electrical failure and large scale release of the excitatory amino acids, glutamate and aspartate. This release of amino acids is associated with calcium influx into the neurones and a cascade of deleterious biochemical events that leads to cell death. The theoretical basis for neuroprotection lies in interrupting this process within the penumbra and reducing the final size of the ischaemic injury. There were initially great hopes for glutamate antagonists, particularly the N-methyl-D-aspartate receptor antagonists. A number of neuroprotectants remain in late clinical development, but many have fallen by the wayside, either through unacceptable side-effects or lack of efficacy. The latest, lubeulizole, a NO modifier, produced conflicting results in very similar trials performed on either side of the Atlantic. Thus far, neuroprotective agents have failed to live up to their promise from animal studies and phase II studies, by not delivering efficacy in phase III.

The early mortality in cerebral ischaemia is predominantly due to swelling of the brain and the development of fatal raised intracranial pressure. This swelling is due to oedema developing in the dead and dying ischaemic areas. A decade ago glycerol was demonstrated to reduce the mortality associated with oedema without increasing the number of disabled survivors. Even more heroic measures such as decompressive surgery for hemispheric infarction have been tried with initially encouraging results (mortality reduced from two thirds to a third).

While in the US thrombolysis is standard treatment for those lucky stroke victims who get to hospital early enough and have no changes on computed tomography, in Europe there is no consensus on acute therapy for stroke. The European license for t-PA use in cerebral infarction is currently under consideration. Why have acute treatments for a relatively simple problem of a blocked pipe in the brain been so problematic?

The terminology has seduced us into believing the problem is simple. The term ‘stroke’ should be exorcised from the medical literature. A stroke is defined as an acute neurological event caused either by cerebral infarction or intracerebral haemorrhage in which symptoms persist for longer than 24 hours or which results in death. The WHO has included subarachnoid haemorrhage as a form of stroke, but many authors do not. From a neuroscientific point of view, the term ‘stroke’ is unsatisfactory in that it includes a number of pathologies whose management and prognosis are different. By using the term there is thus a danger of over simplifying a complex area. Adding qualifiers helps little. Haemorrhagic stroke, which means primary intraparenchymal haemorrhage, is often confused with secondary haemorrhagic transformation of an infarct. The term ischaemic stroke is equivalent to cerebral infarction, but fails to convey the heterogenous nature of the pathology.

When assessing the nature of an acute cerebrovascular event there are several pertinent questions to be answered. First, it must be decided whether it is an infarct or a haemorrhage. If it is a haemorrhage then the underlying cause (hypertensive, arteriovenous malformation, amyloid angiopathy, etc.) must be ascertained. If it is an infarct, the first step is to identify the blood vessel concerned. This involves territory (anterior vs posterior) and size (large artery vs arteriole). Ischaemic events are either transient (symptoms resolving within 24 hours) or not. The second step is to infer the probable mechanism; whether it is likely to be due to hypoperfusion or is embolic or thrombotic. The third step, and most important for long-term secondary prevention, is to identify the underlying pathological process, such as atheroma or hyaline degeneration secondary to hypertension (table). The discharge diagnosis on a patient would then be, for example: “cerebral infarction in the middle cerebral artery territory, presumed to be embolic in nature, secondary to atheromatous disease”. Such a classification requires clinical acumen and access to neuroimaging. A recent audit in our hospital revealed that the assessment by the admitting doctor went no further than ‘stroke’ in 60% of cases (Clinical Audit Department, North Staffordshire Hospital NHS Trust, 1996).

The danger from a clinical point of view of talking about stroke or cerebrovascular disease is that the terms presume a unitary phenomenon. Unsophisticated studies into ‘stroke’ can produce results that are difficult to apply to individual patients.

Meta-analyses demonstrating that organised stroke unit care reduces death, dependency and the need for institutional care, are examples of two heterogenous terms (stroke and stroke unit) held together by p<0.0001. What is it about organised care and which patients benefit? As meta-analysis failed to find any sub-group of patients or model of stroke unit care particularly associated with benefit, one might be tempted to conclude that the

<table>
<thead>
<tr>
<th>Vessel</th>
<th>Mechanism</th>
<th>Pathological process</th>
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<tbody>
<tr>
<td>Carotid</td>
<td>Embolism</td>
<td>Atheroma</td>
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<tr>
<td>Middle cerebral</td>
<td>Thrombosis</td>
<td>Hyaline degeneration</td>
</tr>
<tr>
<td>Anterior cerebral</td>
<td>Hyperfusion</td>
<td>Migrainous</td>
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<td>Basilar</td>
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<td>Atrial fibrillation</td>
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<tr>
<td>Posterior cerebral</td>
<td></td>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>Arterial (location)</td>
<td></td>
<td>Vasculitis</td>
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</tbody>
</table>

Table: Classification of cerebral infarction
advantage was attributable to a general effect, such as staff morale and dedication.

In the general population the word ‘stroke’ raises feelings of doom and passivity. Only 60% of the US population over 50 years old realise that a stroke occurs in the brain.11 If the potential advantages of thrombolysis and neuroprotective agents are to be realised, patients have to receive medical attention rapidly. In order to raise awareness of the urgent nature of the situation the term ‘brain attack’ aptly describes the situation without pretending to be a diagnosis.

The term ‘stroke’ is obscurantist, reductionist, and redundant. It has connotations that are unhelpful to both the general public and the medical profession. Better terms exist that either do not pretend to be a diagnosis (eg, ‘brain attack’), or that have some pathophysiological significance. ‘Stroke’ should be consigned to the dustbin of medical usage.

Those interested in the management of ‘stroke’ were lulled into intellectual complacency by an uncritical acceptance of analogies with myocardial infarction. Cerebral infarction is a much more complex process and requires a more sophisticated approach; a preliminary and necessary step is the discarding of simplistic terminology. We can then concentrate on therapeutic interventions in subpopulations defined by pathology and time from onset.

Simon J Ellis
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Medical Anniversary

Arthur Porritt, 10 August 1900

Arthur Espie Porritt (1900-1994) was born in Wanganui, New Zealand, son of a surgeon. He was a Rhodes Scholar at Oxford, an Olympic athlete, a surgeon at St Mary's Hospital, London, Sergeant-Surgeon to the Queen, the President of the Royal College of Surgeons (1960), Governor-General of New Zealand (1967) and was made a Life Peer in 1973. He died in London on 1 January 1994. — DG James

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