BMJ

LONDON, SATURDAY 15 JULY 1995

Treating acute ischaemic stroke

Still no effective drug treatment available

Now that drug treatment for acute myocardial infarction has been largely sorted out, the world of vascular medicine has moved on to acute stroke. Given that stroke is the third commonest cause of death in the West and the most important cause of adult disability,[1] it is surprising that no treatment exists that has been conclusively shown to reduce the risk of death or disability. Despite a massive worldwide effort to rectify this, early results are disappointing.

In the West most (85%) strokes result from cerebral infarction after arterial occlusion. Ischaemia induces activation of the glutamate-calcium cascade and cytodestructive enzymes, the release of free radicals, and ultimately cell death.[2] Surrounding the core of dead neural tissue lies a penumbra of neurones that may survive or die, which has become the focus of pharmacological activity.

The main classes of agents include thrombolytics (to accelerate reperfusion), anticoagulants and antithrombotics (to prevent further occlusion), vasodilators (to increase cerebral blood flow), antileucocytic drugs (to prevent inflammation), glutamate antagonists, calcium antagonists, and free radical scavengers. Anticoagulants, antithrombotics, and antileucocytic drugs may also reduce the early risk of deep vein thrombosis and pulmonary embolism, which are important complications of stroke.

Two sets of events have occurred recently that considerably advance our knowledge of treatment of stroke. Firstly, the results of several trials of thrombolysis have recently been presented or published (although their interpretation is complex). One study, the multicentre acute stroke trial of Europe, stopped prematurely because of increased early death in patients treated with streptokinase.[3] The Australian streptokinase trial also finished early because patients given thrombolysis between three and four hours after the onset of stroke fared worse than those treated within three hours.[4] The European cooperative acute stroke study of 608 patients reported a non-significant increase in death and severe disability at three months in patients receiving recombinant tissue plasminogen activator.[5] Finally, the multicentre acute stroke trial in Italy has suspended recruitment at 616 patients (of a planned 1200) to await further analysis of the existing data on thrombolysis. A common finding in these trials is that the outcome after thrombolysis seems worse in the first four weeks (with more deaths) but better after three to six months. This is analogous with the results of carotid endarterectomy for severe symptomatic carotid stenosis, which carries a definite early risk but survivors are subsequently relatively protected from ipsilateral stroke.

The second important event is the publication of the *Cochrane Database of Systematic Reviews* on disk, which includes the first set of overviews from the Cochrane Stroke Review Group[6]; six reviews relate to the treatment of stroke, three to secondary prevention in atrial fibrillation, and one each to care in a stroke unit and carotid endarterectomy patch angioplasty.

In contrast to the recent trials of thrombolysis, meta-analysis of six older and smaller studies (899 patients in total) suggests that early thrombolysis results in a non-significant fall in early death (odds ratio 0·62 (95% confidence interval 0·31 to 1·23)) and symptomatic bleeding into cerebral infarction (0·60 (0·21 to 1·67)).[7] An update of this analysis including the recent thrombolysis trials is urgently needed to determine whether further trials of thrombolysis are warranted and, if so, how they should be designed.

An analysis of trials of anticoagulant treatment in which patients were enrolled within two weeks of their stroke suggests that such treatment reduces the risk of deep vein thrombosis (eight trials, 750 subjects; odds ratio 0·18 (0·13 to 0·25)). There was no significant effect, however, on mortality, and a non-significant increase in symptomatic intracranial haemorrhage was observed.[8] Four trials of antiplatelet agents (ticlopidine or aspirin-dipyridamole) have also been reviewed; no significant changes in deaths, deep vein thrombosis, or symptomatic intracerebral haemorrhage were found.[9]

Randomised trials of intravenous epoprostenal showed no effect on deaths at one month.[10] In contrast, intravenous glycerol reduced early deaths (six trials, n=454; odds ratio 0·57 (0·36 to 0·90) but not late deaths.[11] Future reviews by the Cochrane Collaboration will include studies of calcium antagonists, corticosteroids, gangliosides, haemodilution, oxpentifylline, and vinpocetine in acute stroke. It is evident from these systematic overviews that too few patients receiving each potential treatment have been studied and that much larger trials are required. The international stroke trial, the first "mega trial" in stroke, is assessing the effects of aspirin or heparin, or both, on 20 000 patients enrolled within two days of the onset of stroke and will report within 18 months (details on recruitment from Peter Sandercock 0131 343 6639).

Developing drug treatments for cerebral ischaemia will be

far more difficult than for myocardial infarction; 20 years of trials have yet to provide an effective drug treatment for stroke. We will probably have to wait until the next century before treatments other than antithrombotic and anticoagulant treatment (for example, neuroprotection) have been tried in sufficient numbers of patients to assess their efficacy and safety adequately. Sadly, little regard has being given to developing treatments for primary intracerebral haemorrhage, although newer trials of neuroprotective agents (including the planned international stroke trial 2) are starting to include patients with this condition.

To accelerate the development of short term treatments for stroke six actions are necessary. Firstly, hospitals capable of participating in multicentre trials should join them to speed recruitment. Secondly, hospitals will need to open acute stroke units to facilitate such trials[12 13] (much as coronary care units made treatment of myocardial infarction trials possible). Thirdly, most ongoing trials require the involvement of patients within three to 12 hours of the onset of stroke. Patients, general practitioners, and hospital staff need to appreciate that early presentation to hospital will increase the population of patients eligible for, and hence who may benefit from, such trials; the National Institutes of Health's trial of tissue plasminogen activator managed to enrol 300 patients within 90 minutes of the onset of stroke so it is possible to greatly reduce the time that elapses before the initiation of treatment. Fourthly, some trials of drugs that alter haemostasis (especially thrombolytics, anticoagulants, and antithrombotics) require prior computed tomography to exclude primary haemorrhage; the routine availability of 24 hour tomography is now required in all acute hospitals. Fifthly, short term drug treatments for primary intracerebral haemorrhage need to be developed. Lastly, systematic reviews spanning the whole range of the management of stroke are required to help define future lines of research.

PHILIP M W BATH
Wolfson senior lecturer in stroke medicine

Department of Medicine,
King's College School of Medicine and Dentistry,
London SE5 9PJ

1 Bonita R. Epidemiology of stroke. *Lancet* 1992;339:342-4.
2 Pulsinelli W. Pathophysiology of acute ischaemic stroke. *Lancet* 1992;339:533-6.
3 Hommel M, Boissel JP, Cornu C, Boutitie F, Lees KR, Beesson G, *et al.* Termination of trial of streptokinase in severe acute ischaemic stroke. *Lancet* 1995;345:57.
4 Donnan GA, Davis SM, Chambers BR, Gates PC, Hankey GJ, McNeil JJ, *et al.* Trials of streptokinase in severe acute ischaemic stroke. *Lancet* 1995;345:578-9.
5 Hacke W, Kaste M, Fieschi C, for ECASS Study Group. The efficacy of IV-rtPA in acute ischemic stroke: first results of the ECASS trial. *Stroke* 1995;26:167.
6 Counsell CE, Fraser H, Sandercock PAG. Archie Cochrane's challenge: can periodically updated reviews of all randomised controlled trials relevant to neurology and neurosurgery be produced? *J Neurol Neurosurg Psychiatry* 1994;57:529-33.
7 Wardlaw J, Yamaguchi T, del Zoppo G, Hacke W. Thrombolysis in acute ischaemic stroke. In: Warlow C, Van Gijn J, Sandercock P, eds. *Stroke module. Cochrane database of systematic reviews.* London: BMJ Publishing, 1995. [Updated 9 March 1995.]
8 Counsell C, Sandercock P. The efficacy and safety of anticoagulant therapy in patients with acute presumed ischaemic stroke: a systematic review of the randomized trials comparing anti-coagulants with control. In: Warlow C, Van Gijn J, Sandercock P, eds. *Stroke module. Cochrane database of systematic reviews.* London: BMJ Publishing, 1995. [Updated 9 March 1995.]
9 Counsell C, Sandercock P. The efficacy and safety of antiplatelet therapy in acute presumed ischaemic stroke: a systematic review of the randomized trials comparing immediate antiplatelet therapy with control. In: Warlow C, Van Gijn J, Sandercock P, eds. *Stroke module. Cochrane database of systematic reviews.* London: BMJ Publishing, 1995. [Updated 9 March 1995.]
10 Bath P, Bath F. A systematic review of prostacyclin and analogues in acute ischaemic stroke. In: Warlow C, Van Gijn J, Sandercock P. eds. *Stroke module. Cochrane database of systematic reviews.* London: BMJ Publishing, 1995. [Updated 9 March 1995.]
11 Rogvi-Hansen B, Boysen G.l.v. glycerol treatment in acute ischaemic stroke. In: Warlow C, Van Gijn J, Sandercock P, eds. *Stroke module. Cochrane database of systematic reviews.* London: BMJ Publishing, 1995. [Updated 9 March 1995.]
12 Morris AD, Grosset DG, Squire IB, Lees KR, Bone I, Reid JL. The experiences of an acute stroke unit—implications for multicentre acute stroke trials. *J Neurol Neurosurg Psychiatry* 1993;56: 352-5.
13 Bath PMW, Butterworth RJ, Soo J, Kerr J. The King's College Hospital Acute Stroke Unit. *J R Coll Physicians Lond* (in press).

Workplace health in primary care premises

Has been neglected

One of the strategies of the *Health of the Nation* is to improve health in the workplace, especially in NHS workplaces.[1] Health care is labour intensive, so better health of staff should lead to a more effective and economical service as well as directly benefiting employees. Staff sickness in the NHS is not accurately quantified but may cost many millions of pounds annually,[2] much of it being due to avoidable causes such as back injury. As the NHS is founded on primary care one might expect the health of primary care staff, and of their workplaces, to have received particular attention. In fact, it remains underdeveloped and under researched.

This neglect reflects several biases. Firstly, initiatives within the health service have so far concentrated on hospitals, where there is economy of scale and a tradition of managerial control. Secondly, practices interested in ensuring a healthy workplace may not have the greatest need: poorly organised and overworked practices probably have more hazardous premises and their staff probably have worse health. Thirdly, for doctors and dentists one can obtain statistics such as deaths due to suicide or cirrhosis and point to responses such as the sick doctors scheme; but these can seldom be found for other grades of staff. These biases imply a law of inverse care for workplace health in primary care.

The neglect also reflects a curious culture in the workplace. Practices are independent, and their staff are not protected by NHS terms and conditions or by benefits such as NHS superannuation. They have no personnel departments to reconcile employers' and staff interests. They may choose to ignore guidance such as that on no smoking areas[3] or on occupational health.[4] General practitioners are knowledgeable about workplace health because so many consultations raise questions of fitness for work; indeed, many general practitioners have qualifications in occupational health. Yet they face a triple conflict of interest if they act as employer, occupational health medical officer, and family doctor to their own staff. Practice staff work alongside attached community staff, whose working conditions are therefore partly beyond the control of the employing trust, yet who do enjoy NHS benefits. These will include occupational health services, perhaps obtained by the community trust from a nearby hospital, which buys sessions from a local general practitioner. . . .

The "health at work in the NHS" campaign is therefore welcome and timely, but what is in it for primary care? The campaign encourages practical measures such as extending no smoking areas, policies on use and misuse of alcohol, safe lifting and handling, and managing stress. Such measures are not costly, and one might expect that many primary care premises could benefit. Or could they? There are few hard data to bear out this expectation or to ensure that interventions are accurately targeted and sensitive to primary care's needs. The campaign therefore risks missing its mark. The Health Education Authority cites 26 case studies,[2] but only one is based in primary care: a health centre in Essex where reorganised work patterns reduced stress. The associated