- 6 Young GR, Humphrey PRD, Shaw MDM, Nixon TE, Smith ETS. Comparison of magnetic resonance angiography, duplex ultrasound, and digital subtraction angiography in assessment of extracranial internal carotid artery stenosis. *J Neurol Neurosurg Psychiatry* 1994;57:1466-78.
- 7 Mattos MA, van Bemmelen PS, Hodgson KJ, Barkmeier LD, Ramsey DE, Sumner DS. The influence of carotid siphon stenosis on short- and long-term outcome after carotid endarterectomy. *J Vasc Surg* 1993;17: 902-11.

Sellar replies:

I am pleased that Young and colleagues have responded to the review of imaging the blood vessels of the head and neck, as their letter addresses what is the key issue: do the risks of angiography outweigh its benefits when used to select patients suitable for carotid endarterectomy?

In the review my aim was to attempt to achieve a balanced assessment of the current available medical literature on the subject. The views expressed by Young *et al* do, I believe, represent an extreme view of the subject coloured by local experience. They quote their own 4% stroke rate for angiography and have found one other centre (not, incidentally, Edinburgh!) with a similar experience.¹ It is useful to quote this paper in greater detail—"50% stenosis was a significant prediction of risk but the 95% interval of the odds ratio was very wide due to the small total number of complications." The same criticism applies to their own paper, in which two less complications would have more than halved the risk of stroke.

In a recent analysis of the complications of angiography of several large series including our own meta-analysis of eight prospective series² Heiserman *et al* found a mean permanent neurological deficit rate of 1%.³ The 95% confidence intervals of the meta-analysis was less than 2%—0.5% risk of

deficit in the group of patients presenting with stroke or transient ischaemic attack.

The very high complication rate achieved by Liverpool may not only reflect the small group of patients assessed, but other factors. Some of their angiograms were performed by radiologists in training. Mani and Eisenberg found a fourfold increase in complications from angiography in training centres.⁴ Secondly, they included all complications occurring in the 72 hours after the procedure. A significant number of these complications may be unrelated to the angiographic procedure.

On the other hand, their results for non-invasive imaging are unusually good, their combined DUS and MRI misclassifying only 6% of patients whereas the recent meta-analysis of these techniques Young *et al* quotes reports sensitivities of only 83–86% for these techniques.⁵ What Young *et al* did not quote was the conclusion of this meta-analysis: non-invasive tests cannot substitute for angiography as the sole preoperative test for carotid endarterectomy. Non-invasive tests have less than perfect performance at classifying diseased and non-diseased patients. The consequences of misclassification are high; endarterectomy is not an entirely benign procedure.

Let us ignore for a moment those patients who by non-invasive imaging may be led into unnecessary carotid endarterectomy with its 7.5% perioperative stroke rate.⁶ What is the effect of using non-invasive imaging with a sensitivity of 80%? If we make three assumptions relating to these patients with 70% stenosis: that the risk of angiography is 1%, that after surgery there is a 10% risk of stroke over three years, but that patients who have medical treatment the risk of stroke is 20%. The actual ECST figures were 12.3% and 21.9% respectively.⁶ It can be seen that over the three year period (figure) there are 120 strokes in the group using non-invasive imaging and 110 from conventional angiographic work up.

Flow diagram of the consequences of managing 1000 patients with 70% carotid stenosis by conventional angiography (cva) compared with non-invasive imaging. The sensitivity of non-invasive imaging is taken to be 80% resulting in 200 patients having inappropriate medical treatment

Obviously these results would be different if higher sensitivity could be assumed for non-invasive imaging but Blakeley *et al* comments in their meta-analysis that the series he analysed probably contains a publication bias with only specialised centres with respectable results publishing data. This caveat is supported by the NASCET data,⁷ which found only a 59% sensitivity for DUS detecting 70% angiographic stenosis when used in a multicentre trial and the results of Worthy *et al*⁸ who found only a 52% sensitivity for DUS correctly classifying this group. (These results are only just superior to tossing a coin.)

In conclusion, what may happen if we abandon angiography too early? Firstly, we remove the impetus to improve the ability of non-invasive techniques to select those patients who will benefit from carotid surgery, as we remove the only gold standard that has been shown to select these patients. It will quickly become thought to be unethical to test non-invasive techniques against angiography. Secondly, we may be throwing the baby out with the bath water if the non-invasive techniques in non-specialised centres have a sensitivity closer to 60% than 90% as suggested by the NASCET results. Then substantial numbers of patients will be deprived of beneficial carotid surgery as well as other patients having unnecessary surgery. We need to work urgently towards the day when we can put cerebral angiography finally to bed, but to recommend non-invasive imaging for all centres at the present time would be irresponsible.

- 1 Hankey GJ, Warlow CP, Molyneux AJ. Complications of cerebral angiography for patients with mild carotid artery territory ischaemia being considered for carotid endarterectomy. *J Neurol Neurosurg Psychiatry* 1990;53:542-8.
- 2 Hankey GJ, Warlow CP, Sellar RJ. Cerebral angiographic risk in mild cerebrovascular disease. *Stroke* 1990;21:209-22.
- 3 Heiserman JE, Dean BC, Hodale JA. Neurological complications of cerebral angiography. *AJNR Am J Neuroradiol* 1994; 15:1401-8.
- 4 Mani RL, Eisenberg RC. Complications of catheter cerebral angiography: analysis of 5000 procedures, 1: criteria and incidence. *Am J Radiol* 1978;131:867-9.
- 5 Blakeley DD, Oddowe EZ, Hasselbad V, *et al*. Non-invasive carotid artery testing: a meta-analytic review. *Ann Intern Med* 1995;122: 360-7.
- 6 European carotid surgery trialists collaborative group. MRC European Carotid Surgery Trial: Interim results for symptomatic patients with severe (70%–90%) or with mild (0%–29%) carotid stenosis. *Lancet* 1991;337: 1235-43.
- 7 Rankin RN, Fox AJ, Thorpe K, *et al*. For NASCET collaborators. Carotid ultrasound correlation with angiography in a multicentre trial (personal communication).
- 8 Worthy SA, Henderson J, Griffiths PA, Ghohkar A, Oates CP. The role of duplex ultrasound and angiography in the investigation of carotid disease. *J Neuroradiol* 1996 (in press).

Dexamethasone treatment for acute bacterial meningitis: how strong is the evidence for routine use?

In their methodological review of papers reporting clinical trials of dexamethasone treatment for acute bacterial meningitis,¹ Prasad and Haines provide some valuable guidelines for assessment of methodological rigour in studies of the treatment of bacterial meningitis. These points may be useful in

designing future studies to evaluate the use of dexamethasone in bacterial meningitis, were it not for the immense practical difficulties in recruitment for, and conduct of, such studies, which will be made immensely more difficult by the virtual disappearance of meningitis caused by *Haemophilus influenzae* type b in developed countries.

I think that Prasad and Haines, while giving a complete picture of the characteristics of the perfect study, contribute very little to the readers' ability to use the available, if imperfect, data in the most clinically useful manner. The sensitivity analysis shown in table 3 is inappropriate and misleading, even as a worse case scenario. The number of subjects withdrawn from the analysis includes both children who are excluded because of diagnoses other than bacterial meningitis, primarily aseptic meningitis, and children with bacterial meningitis who were lost to follow up. It is clearly unreasonable to equally assign patients with aseptic meningitis to the treatment and control group and then assign all such patients in the treatment group as having had an adverse outcome and all patients in the control group as having had a favourable outcome as it is known that aseptic meningitis is rarely, if ever, associated with adverse sequelae. The only other work presented by the authors is a stratified analysis of the study by Girgis and coauthors which simply confirms that their overall findings of reduced mortality remained after stratification.

In summary, I think that only the most dramatic of treatment benefits in the most rigorous of trials could survive sensitivity analysis as exacting as that tabulated by Prasad and Haines. I do not consider that the results of this sensitivity analysis can reasonably be interpreted as showing lack of demonstrable benefit from dexamethasone in bacterial meningitis. In addition to the concern which the authors rightly have for demonstrating a favourable risk:benefit ratio in a real life clinical setting, there is also the concern that patients may be denied the benefit of an effective treatment which has been discounted by inappropriate and misleading handling of the data.

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- 1 Prasad K, Haines T. Dexamethasone treatment for acute bacterial meningitis: how strong is the evidence for routine use? *J Neurol Neurosurg Psychiatry* 1995;59:31-7.

Prasad replies:

I read with interest the letter by McIntyre. He raises three points: (1) future studies will be difficult because of the virtual disappearance of meningitis in developed countries; (2) our sensitivity analysis is based on "unreasonable" assignment of adverse outcome to the treatment group, particularly for patients with aseptic meningitis and it cannot reasonably be interpreted as showing lack of demonstrable benefit from dexamethasone in bacterial meningitis; (3) the "patients may be denied the benefit of an effective treatment which has been discounted by inappropriate and misleading handling of the data". I take each point in turn.

If bacterial meningitis has virtually disappeared from the developed countries, future studies can and should be undertaken in developing countries where it is still a major public health problem. This is all the more necessary because maximum use of dexamethasone will occur where meningitis occurs. As we have shown in our paper, the studies to date have limited internal validity and generalisability.

Our sensitivity analysis is appropriate and revealing because it shows the weakness of the evidence available on the subject. This is what other authors have also recommended.¹ McIntyre has an incorrect notion about the place and purpose of a sensitivity analysis. Firstly, this kind of analysis is required when authors do not report intention to treat (ITT) analysis or do not provide enough information to allow such an analysis and do not report steps taken to protect their analysis from bias. Most trials of treatments (whether dramatic or otherwise) do carry ITT analysis and therefore, sensitivity analysis is not required. If it is required, its purpose, as reported in our paper, is to assess the robustness of conclusions based on inadequate data and it is not to show the presence or lack of benefit. The inadequacy may be in terms of poor recording of risks or excessive losses to follow up. Almost any drug can be proved beneficial, if patients with adverse effects of the drug are withdrawn from the analysis or adverse effects are not counted. Although patients with aseptic meningitis rarely have a poor outcome, they are not immune to adverse effects of dexamethasone. Certainly, it is not reasonable to assume that all patients with aseptic meningitis given dexamethasone will have an adverse outcome, but to this extent, all sensitivity analyses with worst case scenarios are unreasonable. But it serves its purpose by showing that the published evidence is not strong and that it has not been proved beyond doubt that dexamethasone does more good than harm. However, "absence of proof" is not the "proof of absence". If we wish to base our practice on stronger evidence—as we should—we need more studies and proper analysis of the primary data collected from the investigators in both directions. We and some investigators in Holland are conducting randomised trials of dexamethasone in adults with bacterial meningitis and a Cochrane review of the primary data is planned.

The third point by McIntyre is more profound. It has at its heart questions such as: "is it unethical to withhold a potentially effective treatment the risk-benefit profile of which is not studied adequately?"; "when are randomised trials of a treatment unethical?"; "when is the evidence good enough to make strong recommendations?" and so on. These are issues about the science and ethics of practice of medicine. The available space will not allow me to do justice to the issues involved. I will simply state that until we have shown "a favourable risk-benefit ratio of a drug in real life clinical setting," there is no justification to subject all our patients to risk of adverse effects of the drug except in randomised trials. It is true that "ways of science" and evidence (randomised trials being the best method) do require denying some patients what may turn out to be beneficial, but the other way—policies advocating clinical use of a drug without proper evaluation of the risk-benefit ratio—is far too dangerous to be acceptable.

- 1 Guyatt GH, Sackett DL, for the Evidence-Based Medicine Working Group. Users guides to the medical literature, II: How to use an article about therapy or prevention, A: Are the results of the study valid? *JAMA* 1993;270:2598-601.

NOTICE

Announcement from the British Neuro-psychiatry Association: 1996 summer meeting

The 1996 Summer meeting will be held on 14-16 July at Robinson College, Cambridge. It will include topics on neuro-development, language, and the presentation of short scientific papers and single case videos by members. The Association's AGM will be held on 16 July.

For further details of these meetings please contact: Sue Garratt, Administrative Assistant, BNPA, 17 Clocktower Mews, London N1 7BB. Telephone/Fax: 0171 226 5949.

For details of membership of the BNPA, which is open to medical practitioners in psychiatry, neurology, and related clinical neurosciences, please contact: Dr Jonathan Bird, Secretary BNPA, Burden Neurological Hospital, Stoke Lane, Stapleton, Bristol, BS16 1QT. Telephone: 01179 701212 ext 2925/2929 or Sue Garratt at the address given above.

BOOK REVIEWS

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Atlas of Human Spinal Cord Evoked Potentials. Edited by MILAN R DIMITRIJEVIC and JOHN A HALTER. (Pp 180; £50.00). Published by Butterworth Heinemann, Oxford 1995. ISBN 0-75069631-1.

This is a multi-author book comprising a reference text for those readers with a highly