COMMENTARY

Carotid endarterectomy

See page 1491

A half-century ago the first surgical procedure to prevent stroke was reported in *The Lancet*.[1] The patient in this epochal advance had had neurological symptoms in the carotid territory of the brain and angiography of the relevant carotid artery, which revealed stenosis.. The concept proved eruptive: within 25 years an estimated 1 million carotid endarterectomies had been done, mainly on patients with neurological symptoms (stroke or transient cerebral arterial ischaemia) who were then investigated angiographically, revealing stenosis. Ultrasonography extended the procedure to the potentially much larger population with asymptomatic lesions. The notion was explored that patients with only vertebral/basilar symptoms might benefit from carotid endarterectomy performed on asymptomatic carotid stenosing lesions. The results failed to be convincing of secondary benefit transferred from one arterial territory to another. Interest dwindled.

From the mid-1950s until 1981, claims of benefit were anecdotal with inexact historical comparisons. Ultimately patients with symptomatic and, later, with asymptomatic lesions entered large randomised trials. The North American Symptomatic Carotid Endarterectomy Trial (NASCET)[2] and the European Carotid Surgery Trial (ECST)[3] proved that with hemisphere or ocular neurological symptoms associated with over 70% carotid stenosis, identified by angiograms, benefit from careful carotid endarterectomy was unequivocal, despite a 6% perioperative risk of stroke or death. The greatest gain was in men, the elderly, and patients with hemisphere and not solely retinal symptoms. Only six patients needed to be treated to prevent one stroke in 2 years. For symptomatic patients in NASCET with only 50–69% carotid artery stenosis (in whom stroke risk is less than in patients with greater stenosis) and with perioperative risk of 6% the number needed to treat to prevent stroke was 15. By comparison, in ECST, an 8% perioperative risk nullified the net benefit, which is a stark reminder that operative risk is critical in carotid endarterectomy where the complications are the same as what one is attempting to prevent.[4]

In patients with 60–99% carotid artery stenosis but, as yet, no neurological symptoms (such as stroke or transient cerebral ischaemia), the Asymptomatic Carotid Atherosclerosis Study (ACAS),[5] from North America, detected only modest benefit favouring carotid endarterectomy. The 30-day combined risk of stroke and death from angiography and surgery was 2·3%. The absolute risk-reduction projected to 5 years was 5·9%. The number needed to treat to prevent one stroke in 2 years was at least 67. The benefit did not seem to depend on the severity of the stenosis, as measured by ultrasound alone. Small numbers of events in ACAS probably explain the lack of demonstrable benefit for women or for disabling stroke.

Today's *Lancet* presents results of the latest and largest asymptomatic trial, the Asymptomatic Carotid Surgery Trial (ACST). With increased numbers of patients and outcomes, modest benefit extended to women and disabling stroke. Surgical morbidity and mortality was 3·1%. The absolute risk reduction at 5 years was 5·4%.

Before concluding that the route has been cleared to the operating room for most patients with asymptomatic carotid stenosis, several factors require careful consideration. First, patients must recognise that with good medical care they face only a 2% annual stroke rate, which falls below 1% after successful carotid endarterectomy. But the benefits will exceed the risks only if the operative hazards remain low, otherwise they could be obliterated. Contemporary reports suggest that the rates of operative complications often exceed by 1 or 2% the low rates achieved by trial surgeons (3%).[6,7] Thus, if such surgery is to be offered, audited results of surgeon's operative records should be readily available to referring physicians and patients. Institutions and departments should require totally independent audits of surgical morbidity rates and ensure their ready availability. Experts in examining the nervous system should be required to evaluate the postoperative condition of all patients who have carotid endarterectomy.

Second, despite the disclaimers in the ACST report, scrupulous and compliant regulation of lipids, glucose, blood pressure, cigarette smoking, and appropriate platelet inhibition would narrow the medical/surgical gap. Evaluation of this possibility requires a stricter protocol than has yet been used.

Third, uncertainty surrounds the failure of both of the trials in asymptomatic patients to find any difference between the higher and lower deciles of stenosis, as assessed by ultrasound. By contrast, both of the trials in symptomatic patients found strikingly greater risks from unoperated lesions, and correspondingly greater benefits from successful carotid endarterectomy in patients with the higher (>70 %) degrees of stenosis.. All the patients in the symptomatic trials had their stenosis assessed by conventional angiography, suggesting that failure to detect the relevance of the stenosis in the asymptomatic trails might merely reflect the imperfections of ultrasound as a sole technique of measurement.[8,9] The search for those asymptomatic individuals who are, if untreated, at highest risk must continue on several fronts, including the use of modern non-invasive imaging methods. Patients with reliably identifiable severely stenosing lesions will probably be found to benefit the most.

Fourth, unlike all the other large trials, in ACST the main analyses of the effects of surgery involved not only ipsilateral but also contralateral strokes. No comparative curves were presented for just ipsilateral carotid territory ischaemic strokes, which are the type most expected to be reduced by operating on one diseased artery. The striking statistical observation that contralateral strokes were significantly reduced by ipsilateral carotid endarterectomy cannot yet be promised to patients as a bonus benefit. Detailed imaging observations on the contralateral artery, perfusion studies

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both preoperatively and postoperatively, study of the collateral blood flow, and careful surveillance for potentially embologenic lesions of heart and aorta must be part of an ongoing evaluation of this unexpected but intriguing observation.

Problems persist, but the investigators of the ACST are to be congratulated for performing well a monumental task. They are to be commended for their cautionary concluding remarks. Carotid endarterectomy with any less skill than exhibited by ACST and ACAS surgeons quickly casts the procedure into the list of "risk factors for stroke".

I have no conflict of interest to declare.

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Diagnosis of lung rejection

See page 1503

Lung transplantation is entering an exciting era. Better preservation of organs, expanded criteria for donors, and improved understanding of events during reperfusion resulted in a 23% increase in activity and a fall in 30-day mortality in the UK. The chance of early death was lower than that for cardiac and hepatic transplants in 2002–03.[1]

This optimism has not yet extended to the longer term. The subsequent rate of attrition is higher for the lung than for other solid organs, with registry data still recording a 5-year survival little better than 50%,[2] and under a fifth of patients surviving 10 years. Most late deaths are due to progressive narrowing of small airways, described histologically as obliterative bronchiolitis and functionally as a fall in forced expiratory volume in 1 s and defining the bronchiolitis obliterans syndrome. This syndrome is thought to represent airway remodelling as a response to various epithelial injuries. This theory accommodates non-immune risk factors such as organ ischaemic time, donor age, and infection with cytomegalovirus, but by far the most important predictor is early acute rejection. Most of the airway injury is probably immune-mediated and control of early rejection is key to the prevention of bronchiolitis obliterans syndrome.

The diagnosis of early rejection is difficult. Clinical and radiological features—high temperature, hypoxia, and alveolar infiltrates—are non-specific and are shared with reperfusion injury and, in particular, infection. The gold-standard diagnosis uses transbronchial biopsy, but this procedure carries a risk of bleeding and pneumothorax and can precipitate reventilation of an already compromised patient.[3] At least five, and some say 10–12, specimens are required to overcome sampling errors,[4] and additional bronchoalveolar lavage is required to exclude most infections. The risks make frequent repetition of transbronchial biopsy unjustifiable, and thus true surveillance of rejection in these patients has never been possible. Indeed the situation is so unsatisfactory that some groups have all but abandoned routine transbronchial biopsy, and yet report entirely satisfactory results.[5]

Thus the report in this issue of *The Lancet*, by Seyedhossein Aharinejad and colleagues, of a new diagnostic method is welcome. They describe simple measurement of serum levels of hepatic growth factor as a marker for lung rejection. Increased concentrations preceded rejection (confirmed histologically or as a favourable therapeutic response), with a fall after treatment. There was good discrimination of infection, although the incidence of viral (in particular cytomegalovirus infections) was very low. This low rate might just represent what can now be achieved by diligent use of powerful and biologically available antiviral prophylaxis.

In addition to the practical day-to-day management of our transplant patients, these observations, if validated by other groups, might have other and potentially far-reaching uses. For no other transplanted organ is there the prospect of a daily test that could be used to map the ebb and flow of interaction between host and graft. Immunological monitoring, the quantification of both the degree of immunosuppression and the host response, is cumbersome and non-specific.[6] A reliable and repeatable measure of effect on the graft would give a realistic perspective to such monitoring.

The next step would be to stratify patients by the vigour of the response and move towards individualising immunosuppression. The observation[7] that different functional polymorphisms in the toll-like receptor 4 defined groups with widely differing rejection rates is an exciting pointer in this direction. In this respect it would be important to demonstrate that levels of hepatic growth factor mirrored acute rejection triggered by innate immunity as well as by conventional pathways.

In Aharinejad and colleagues' study, hepatic growth factor was raised early after transplantation. There is no information about correlations with early performance of the lung. But given that hepatic growth factor is released in response to lung injury, the cytokine should also be investigated as a potential marker of graft dysfunction, currently defined rather non-specifically in terms of gas exchange.

The real test, however, will be in the effect of measurements of hepatic growth factor on late mortality. Despite the correlation between early rejection and bronchiolitis obliterans syndrome, no one has shown clearly that reduction in rejection rates has a positive benefit on the prevalence of the syndrome. If early treatment of rising levels of hepatic growth factor, before significant airway injury occurs (surely the next study to do) reduces the incidence of bronchiolitis obliterans syndrome, Aharinejad and colleagues will have made a real contribution to the major clinical problem in lung transplantation.

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