family with the APP670/1 mutation, the age range at onset for 3 individuals with the ε2/ε3 genotype was 57-60 and for 3 who were ε3 homozygous, it was 51-54. The individual with this mutation who was ε4 homozygous had the earliest onset (44) within the family. These data provide circumstantial evidence that the ε2 allele may protect against disease development. In individuals with APP717Val→Ile, the single individual (out of 9) who is ε3/ε4 heterozygous has the youngest onset (50), and an onset that is outside the range of the other (53-61, mean 56, SD 3).

These data corroborate the statement that ε4 genotypes predispose to earlier onset-ages in families with APP mutations2 and support the notion that ApoE is an important determinant in Alzheimer's disease.1,3

Work in the authors' laboratories is supported by grants from the MRC, the David and Frederick Barclay Foundation, the MFR, the NIA (ROI AG1187-01), and by private donations. We thank the family members for their support and enthusiasm for the programme, and Dr Allen Roses, Dr Dmitry Goldgaber, and their colleagues for pre-publication data.

Alzheimer's Disease Collaborative Group*
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Sir—Alzheimer's disease affects 3-10%, of the population over the age of 65, and approximately half of all cases are familial.1 The frequency of the ε4 allele of the apolipoprotein E (apoE) gene is increased in familial Alzheimer's disease.2,3 The apoE gene on chromosome 19 has three common alleles (ε2, ε3, and ε4), which encode three major apoE isoforms. We aimed to assess the degree to which the presence of ε4 and family history increases the risk for Alzheimer's disease.

The study included 53 families selected for having two or more affected relatives and average age of dementia onset over 60 years.3 NINCDS-ADRA guidelines were used for diagnosis, and 31 families had neuropathological documentation of Alzheimer's disease. We randomly chose 1 patient per family, so that the frequency of ε4 in the cases would not be inflated by the genetic relation among them. 56 non-demented and unrelated spouses, aged 49-90, were used as controls. All subjects were white and of mixed European origin.

Among the 53 cases, 45 were ε4-positive compared with 16 of the 56 controls. The odds ratio estimate was 13.1 (95% CI 5.2-33.3), suggesting that the risk of Alzheimer's disease is increased threefold in the presence of ε4 and family history. The attributable fraction was estimated as 0.78 (95% CI 0.61-0.90), implying that 78% of cases would not have occurred if ε4 were absent in these families.

The odds ratio approximates the relative risk but when the disease is common, the odds ratio may overestimate the relative risk. To investigate this potential bias, we used 5% as the upper estimate for the prevalence of familial Alzheimer's disease and calculated the relative risk as 12.3, close to the estimated value of 13.1.

The ε4 frequency in our familial Alzheimer's disease patients was similar to the frequency in such patients studied by Strittmatter et al,2 and the ε4 frequency in our controls was similar to the reported population frequency of ε4 in US whites.3 When we used the "old" subjects (45-71 years) from the Framingham Offspring Study4 as controls, we estimated the odds ratio as 16.5 (95% CI 7.6-35.7) and attributable fraction as 0.80 (95% CI 0.62-0.89).

Despite the striking measures of association we estimated, the presence of ε4 may be neither necessary nor sufficient for the development of Alzheimer's disease. If ε4 is involved in the pathogenesis of this disease, another risk factor must exist to account for the ε4-positive individuals who live long and remain unaffected, and for those who lack ε4 and yet develop Alzheimer's disease. Alternatively, ε4 may be a marker in close linkage with the disease gene. Irrespective of whether or not it is directly involved in Alzheimer's disease pathogenesis, ε4 in combination with a positive family history is a strong predictor of AD.

The study was financially supported by NIA grants AG08017 (Alzheimer's Disease Center in Portland, Oregon) and AG08017 (Alzheimer's Disease Center at the University of Washington), the American Health Assistance Foundation (TDB, GDS), the Medical Research Foundation of Oregon (HP), and VA Medical Research Fund (TB).

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Immediate intracardiac adrenaline injection in asystole

Sir—O'Nunain and Ruskin (June 26, p 1641) mention only two routes of drug administration (endotracheal and intraosseous) in cardiac arrest if immediate intravenous access cannot be achieved. The intracardiac route is omitted, possibly unintentionally. However, we have used this route several times with successful return of circulation.1 We prefer to inject at a site just to the left of the sternal margin in the 4th or 5th intercostal space. The distance from the left margin of the sternum to the internal mammary artery ranged in 28 males from 1.25 to 1.80 cm and in 12 females from 0.95 to 1.25 cm, with a mean value of 1.48 cm.2

The use of intracardiac injection of adrenaline to restore heart action has long been advocated.3 Davison et al4 evaluated 53 patients who received 147 intracardiac injections during cardiopulmonary resuscitation. Pericardial effusion was noted

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in 6 of 17 echocardiograms and a haemopericardium found in 8 of 28 necropsy specimens. Cardiac tamponade was not recorded. Pneumothorax developed in 1 patient. No necropsy disclosed coronary artery or ventricular lacerations. Amey

found no more complications in patients who received intracardiac medication before admission by paramedics than in controls. When patients are in asystole every second counts—and the chance of return of circulation by the immediate intracardiac adrenaline injection should not be excluded.

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Nasal ventilation in acute ventilatory failure due to chronic obstructive airways disease

Sir—Bott and colleagues (June 19, p 1555) look for benefit from the addition of nasal intermittent positive pressure ventilation to the usual management of chronic obstructive airways disease (COAD) with acute respiratory failure. They do not state when the deaths occurred. Nor do they state how many of the control patients required intubation at some point. This information is quite important since, from figure 1, we see that the degree of acidosis present after 1 hour of treatment in several controls seems to warrant intubation and ventilatory support. Bott and co-workers point out that it was impossible to have any blinding. However, they should indicate the criteria of the treating physicians for instituting endotracheal intubation and ventilatory support, both in the controls and in the group already treated with nasal ventilation. A delay in intubation due to the existence of the study might have contributed to some of the excess deaths.

Bott and colleagues imply that the study was done in the general ward setting. Although this setting would be appropriate for stabilised patients chronically treated with nasal ventilation or for patients in whom full resuscitation is not thought appropriate, I have concerns about the adequacy of the general ward setting for the stabilisation of patients with significant respiratory acidosis.

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Authors’ reply

Sir—The deaths of the patients in the control group took place on days 1 (3 patients), 3 (3 patients), 5 (2 patients), and 8 (1 patient) after endotracheal intubation. The deaths of the patients in the nasal intermittent positive pressure ventilation (NIPPV) group occurred on days 1 (1 patient, unable to take NIPPV) and 2 (2 patients, 1 of whom refused NIPPV). 2 controls needed endotracheal intubation, as we say in our results section.

The criteria for endotracheal intubation were: (1) failure to respond to the instituted therapy in terms of correction of pH and arterial blood gas tensions, and (2) in the presence of (1) the patient being deemed by the responsible clinician to have a reasonable chance of being successfully weaned from traditional ventilatory support and of having a reasonable quality of life in this event. Any patient fulfilling these criteria was offered this form of ventilatory support (2 patients).

It should be clearly stated that, apart from those patients with any of the exclusion criteria stated in our patients and methods section, all patients with an acute admission due to chronic obstructive airways disease were entered in this study. Many of these patients were elderly and had minimum exercise tolerance, even when well. In these patients the clinical judgment was not to institute endotracheal intubation and full resuscitation techniques should the situation arise. The existence of the study in no way jeopardised any patient’s clinical treatment and did not contribute to delay in endotracheal intubation in any patient of either group.

Our collective experience is that the general ward setting can frequently be suitable for the treatment of patients, even those with severe respiratory acidosis, should the clinical decision be made not to institute full resuscitation. In particular, we now rarely move patients requiring NIPPV to the intensive care unit, even when severely compromised, since the technique is so successful in situ. This success is largely attributable to the competence of physiotherapy and nursing staff, as well as the medical staff, in the technique.

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Brain infarction and neck calisthenics

Sir—A 44-year-old Chinese man routinely practised taiqi qiang calisthenics to relieve musculoskeletal pain. On Feb 23, 1992, he did neck circumduction-rotation for high neck pain, and 10 min later had occipital and left temporal headache. He continued calisthenics daily despite headache, blurring of vision, and forgetfulness. 6 days later the patient saw a neurologist, who suspected systemic vasculitis after finding only “ischaemic foci in the thalami, cerebellum, and midbrain” on magnetic resonance imaging (MRI).

The patient continued calisthenics until admission on March 12, 1992. He had no history of migraine, smoking, or regular medication. He was normotensive and alert with impaired short-term memory. He developed dysphasia, cerebellar dysfunction, and right hemiparesis with facial palsy. Four vessel angiography and two-dimensional echocardiography were normal. However, MRI showed eccentric signal-voids in the basilar artery, and the left internal carotid artery and both vertebral arteries in the neck. There were also several 2–8 mm voids in both thalamus, the left internal capsule, midpans, and cerebellum. Cerebrospinal fluid, blood count, erythrocyte sedimentation rate, serum lipoproteins, blood clotting, and serum antithrombin III, protein S, and protein C were normal. Lupus anticoagulant and serum antiphospholipid, antinuclear, and anti-double-stranded DNA antibodies were absent. Treatment consisted of avoidance of neck twisting, stroke rehabilitation, and ticlopidine 250 mg daily. The patient achieved 80% neurological recovery over a year.

Taiqi neck-twisting probably caused subintimal dissection in three neck arteries and multifocal thromboembolic brain infarction in a healthy man. The forces generated by coughing, neck rotation,1 and chiropractic manipulation2 can shear the intima even in angiographically normal neck arteries.3 Head or neck ache may be the only symptom of dissection.4 So the patient’s first neck pain may have marked “spontaneous” dissection. This, however, often affects a single vessel; moreover, some patients overlook trivial neck motion occur-