inhibitors (antithrombin III) are nowadays mandatory before the diagnosis of DIC can be made. Finally, the administration of fresh frozen plasma tends to aggravate DIC rather than controlling the haemostatic defect. The observed haemorrhage may therefore result from local surgical factors rather than systemic coagulation defects.

Changes in haemostasis including increase of fibrinolysis and decrease of plasma fibrinogen and blood platelet count, are not uncommon during and immediately after surgery, and were reviewed by Owen and Bowie.² The effects of cranial surgery upon coagulation have been studied less frequently. Coagulation defects have been observed after neurosurgery,³ increase of blood coagulation activity was reported after removal of meningiomas,⁴ and DIC was observed after removal of an oligodendroglioma.⁵

Mattock and Crockard state that a prospective study of coagulation during intracranial surgery is indicated. Such a study was performed recently, although not exclusively in patients with acoustic neuromas.⁶ In this study coagulation abnormalities occurred in the majority of patients, and more often than observed after general surgical procedures. There seemed to be a relationship between the extent of the intracranial procedure and the extent of the coagulation changes. Removal of deeply situated tumours, which necessarily involved more manipulation and damage of brain tissue than surgery of superficially situated tumours or extracerebral surgery, tended to be associated with a larger increase of FDP concentration, and with a decrease in plasma fibrinogen concentration. Damage to brain tissue, brain tumour cells, and blood vessels may lead to the liberation of thromboplastic material into the circulation, and, subsequently, to the conversion of fibrinogen into fibrin. Finally, fibrinolysis may result in an increase of FDPs. It might well be that the introduction of CUSA (Cavitron Ultrasonic Surgical Aspirator) contributes to an increased release of thromboplastic material into the circulation, and thus to an increased occurrence of coagulation changes during and after neurosurgical procedures. The exact nature of the coagulation defect after neurosurgery however, still needs to be defined.

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Mattock and Crockard reply:

We are grateful to Drs Van der Sande and Buller for their comments and helpful criticism.

Our intention was to raise doubt as to whether all bleeding during and after excision of large (diameter greater than 4 mm) acoustic neuromas was due entirely to failure of surgical haemostasis. It is our impression, and that of other neurosurgeons (personal communications), that in some cases bleeding occurs which cannot be readily explained on the basis of operative technique alone.

We fully accept that the supporting coagulation data in our original report were inadequate to make a diagnosis of disseminated intravascular coagulation (DIC). At the time we did not have the facility for more complex measures of haemostatic function. It was for this reason that we posed the question in the title and proposed that a formal systematic study be undertaken.

Happily we now have access to a specialised haemostasis laboratory and have embarked upon a prospective study. To date we have assessed 10 patients with acoustic neuroma during and immediately after surgery, and have included serial assays of platelet count, fibrinogen, prothrombin time, partial thromboplastin time, thrombin time, fibrin degradation products (FDPs), antithrombin III (ATIII) and Factor VII activity.

In contrast to our initial suggestion we have found so far no convincing evidence of

DIC. There are modest falls in platelet count, fibrinogen and ATIII during and after surgery, and only trivial rises in FDPs. However, one of the 10 individuals required re-exploration for intracranial bleeding and although he had no laboratory evidence for DIC he had a Factor VII level at the time of bleeding of only 0.41 IU/ml (normal range 0.5-2.0 IU/ml), which fell to 0.31 IU/ml a few hours later. Despite infusions of fresh frozen plasma the Factor VII level remained around 0.30 IU/ml for the next 12-24 hours.

As Factor VII is not consumed during normal coagulation, a low Factor VII level does not represent intravascular coagulation, but implies binding of the factor to tissue thromboplastin, either in the circulation or locally at the operative site. Such binding and depletion of Factor VII may encourage operative or postoperative haemorrhage. Although we wish to finish our study before formally reporting, it is possible that Factor VII depletion may be a mechanism for bleeding in some patients with acoustic neuroma, and theoretically for other neurosurgical patients.

Apnoea testing to confirm brain death in clinical practice

Sir: We read the paper by Van Donselaar *et al*¹ with great interest and are not surprised to learn of their failure to raise the pCO₂ of their six patients to 7.98 kPa (60 mm Hg) during apnoea testing. Their data indicate that all of their patients were hyperventilated (presumably to reduce intracranial pressure), resulting in a mean start-of-test pCO₂ of 2.8 kPa (21 mm Hg). It has been our experience, and the experience of others,²⁻⁴ that when the apnoea test is begun with the patient's pCO₂ in the hypocapnic range, the pCO₂ often does not reach 7.98 kPa (60 mm Hg) after 10-15 minutes of apnoea. This failure to reach the target pCO₂ value using the "USA" recommendations is due to the fact that these recommendations do not specify a starting pCO₂.⁵

It has been both our practice and recommendation⁶⁻⁸ to adjust the patient's minute ventilation so that the start-of-test pCO₂ is 4.79 kPa (36 mm Hg) or higher. Using this protocol, our patients exceeded the target pCO₂ of 7.98 kPa (60 mm Hg) in 27 of 28 apnoea tests of 10 minute duration. Our one patient failing to reach the target pCO₂ was relatively hypothermic (35.5

degrees C) when compared with our other patients at the time of apnoea testing.

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van Donselaar et al reply:

We completely agree with the comments made by Belsh and Schiffman. In the discussion-section of our paper we stated that the low pCO₂ levels at the onset of the apnoea test might explain the insufficient levels after 10 minutes of apnoea. We also agree with their recommendation to adjust the minute volume prior to disconnection if the pCO₂ is rather low. In a recent article for the journal of the Dutch Medical Association,¹ we advised the following:

- (1) if the pCO₂ ≥ 5.0 kPa (38 mmHg)
 - preventilate with 100% O₂ for 10 minutes
 - disconnect the patient for 14 minutes while giving O₂ via an endotracheal tube at a rate of 6 litres/min
 - after drawing blood for blood gas determination re-connect the ventilator.
- (2) if the pCO₂ < 5.0 kPa (38 mmHg)
 - preventilate with 100% O₂ for 5 minutes

- continue ventilating with 100% O₂ with a halved volume for 15 minutes
- disconnect the patient for 14 minutes while giving O₂ via an endotracheal tube at a rate of 6 litres/min
- after drawing blood for blood gas determination re-connect the ventilator.

With this method, the pCO₂ will have risen to 7-98 kPa or higher in most patients, while adequate oxygenation is secured.^{2,3} The test must be terminated in case of ventricular arrhythmias of hypotension. In our opinion blood gas determination at the end of the apnoea test is mandatory to see whether the pCO₂ has reached the target value providing supramaximal stimulation of the respiratory centre. For patients with chronic lung disease we refer to the article of Rohling.⁴

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Sino-atrial block provoked by carbamazepine

Sir: Stone and Lange¹ have reported in your Journal the occurrence of ventricular asystole followed by syncope and death in a patient treated with carbamazepine for temporal lobe seizures. They also mention the occurrence of sinus bradycardia due to carbamazepine.

The following case confirms that carbamazepine may cause sino-atrial block. A 54 year old female suffering since the age of 32 from complex-partial seizures with automatisms with a frequency of about 3-5 per day, had been taking carbamazepine 1200 mg/day for one year with a plasma concentration of 6.3-9.0 µg/ml. The epileptic nature of seizures was documented by simultaneous ambulatory EEG and ECG

monitoring; there were no secondary cardiac arrhythmias during the epileptic attack. She was hospitalised after falling from a small ladder without loss of consciousness while housekeeping. On admission, heart rate was 36 per minute and ECG showed rare, isolated monomorphous ventricular ectopic beats. Carbamazepine was discontinued. Pulse rate remained around 40 for a few hours and went back to normal the day after. During the following months the patient was unsuccessfully treated with phenytoin, clonazepam and phenobarbital in combination.

Carbamazepine treatment was resumed at the initial dosage of 150 mg, gradually increased to 300 and then 600 mg over a 4-month period, under weekly ECG controls. There was a considerable decrease in seizures. The patient had been taking 600 mg for 15 days when ECG evidenced a 2:1 sino-atrial block. Plasma concentration was not obtained. Discontinuation of the drug resulted in the disappearance of the arrhythmia in 24 hours. Follow-up examinations on the 3rd, 7th and 14th day did not show any conduction disorder.

Stone and Lange collected nine cases of conduction disorder due to carbamazepine. We may add the present case and a case of sino-atrial block reported by Meyrignac *et al.*² Given the wide application of this drug, the risk of cardiac complications seems low, and carbamazepine remains an excellent anticonvulsant medication.

Blumhardt *et al.*³ have demonstrated by simultaneous EEG and ECG monitoring that temporal lobe seizures are associated with increased heart rate in 24 out of 26 patients. In a series of 16 partial complex epileptic patients monitored in our laboratory⁴ we have observed ictal tachycardia in 13; in two patients there was ictal bradycardia, starting 6-8 seconds from the beginning of the attack and attaining 15% and 53% of the basal frequency. Blumhardt *et al.*³ actually suggest that antiepileptic medication may protect against the risk of sudden death in epileptic patients. The relationship between epilepsy, drugs and the heart must be therefore evaluated in the single patient. However, the need for cardiological examination during carbamazepine prescription, emphasised by Stone and Lange,¹ cannot be overstressed. The use of the drug should be cautious in patients with sick sinus syndrome or blocks at any level. Special attention must be given to elderly patients, who more frequently suffer from these diseases.

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