Letters to the Editor

THERAPEUTIC SUGGESTIONS DURING GENERAL ANAESTHESIA

SIR,—I was disappointed in Mr Evans and Dr Richardson's report (Aug 27, p 491) on therapeutic suggestions during general anaesthesia.

The mechanisms of general anaesthesia are complex and poorly understood. There are also as many anaesthetic techniques as there are anaesthetists. The dismissal of technique by reporting the use of thiopentone and inhalational agents is not good enough. Were benzodiazepenes used for premedication or as part of the anaesthetic? Since some muscle relaxants have metabolites with central nervous system activity, what drugs of that group were used? The reported evidence does not satisfy me that the two groups had similar anaesthetics.

If messages given to anaesthetised patients "get through" in some way, then why was there no difference in postoperative nausea? This side-effect can be reduced by positive messages given to the patient at the anaesthetist's pre-operative visit and is therefore subject to manipulation psychologically. Perhaps this was confounded by non-standard anaesthetic techniques. On the other hand, I would be surprised if the suggestion tape included an instruction to have a short period of postoperative pyrexia. If the tape did, and this effect was one of the dependent variables with a significant difference between groups, Evans and Richardson would surely have said so. Maybe the finding is spurious.

Since the suggestion group almost all guessed correctly that they had heard the suggestion tape I question how blind the study actually was. Presumably the patients gave informed consent; therefore they knew what the study involved. Thus recognition that they were in the suggestion group may have influenced subsequent performance.

A minor point—the description of anaesthetist's experience in table I show only 18 patients in the suggestion group when the head of the table shows n = 19.

Evans and Richardson, as with a number of previous researchers, have fallen into the trap of studying two things at once. The questions I would like to know the answers to are: "Do intraoperative messages help people to recover and heal faster or better after surgery?" and "Do messages given to anaesthetised patients lodge within their minds for later recall or access?". These need to be answered separately since they tend to confuse each other. The evidence that the answer to the second question is "yes" is so subtle (eg, Bennett et al[1]) that the answer must be "no, most of the time". The first question may be more simply answered by a study on unsedated patients undergoing surgery with regional anaesthesia.

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1. Bennett HL, Davis HS, Giannini JA. Non-verbal response to intraoperative conversation. *Br J Anaesth* 1985; 57: 174–79.

*** This letter has been shown to Mr Evans and Dr Richardson, whose reply follows.—ED. L.

SIR,—Our study demonstrated that therapeutic suggestions played to anaesthetised patients may improve the quality and reduce the duration of recovery from surgery. The table shows the volatile anaesthetic agents, induction agents, muscle relaxants, and opioids administered—both groups received similar anaesthetics. We disagree with Dr Mackie that differences in normal anaesthetic practice between two randomly allocated groups could cause the large and highly significant differences that we observed. We evaluated a simple addition to normal clinical practice; a standard anaesthetic technique, as suggested by Mackie, would have reduced the clinical significance and external validity of our findings.

AGENTS ADMINISTERED BY THE ANAESTHETIST*

Drug	Control group	Suggestion group
Induction agents		
Thiopentone	20	19
Midazolam	0	2
Neuromuscular blockade		
Vecuronium	9	12
Suxamethonium	4	4
Curare	5	3
Pancuronium	4	1
Atracurium	2	0
Volatile anaesthetics		
Enflurane	18	15
Halothane	2	4
Opioids		
Fentanyl	18	17
Other	2	2

*This table corrects an error in our report about the frequency of enflurane and halothane use.

There are many possible reasons why the reduction in nausea in the suggestion group did not reach statistical significance. For example, our assessment of nausea may not have been sufficiently sensitive or the variation in individual susceptibility may have been large. The negative result in no way implies that the therapeutic suggestions were not registered by the patients during surgery; indeed it is clear from our other findings that these suggestions did "get through in some way" and did improve recovery from surgery. Mackie suggests that the 45% reduction in the duration of pyrexia in the suggestion group compared with the control group ($p < 0.005$) may have been "spurious". He does not explain how this could be and the odds are more than 200:1 against. Mackie correctly assumes that the tape did not include an instruction to have a short period of postoperative pyrexia. We do not believe that such an instruction would be helpful, but the tape did include three different types of suggestion which may have reduced pyrexia by the mechanisms we discussed.

The study was double-blind until after the patient was discharged from hospital. The anaesthetists did not detect any signs of awareness during surgery, the tapes were played only during the deepest period of anaesthesia, and no patient could recall any intraoperative events or sounds. Despite this amnesia all but one of the suggestion-group patients guessed correctly that they had been played an instruction tape during surgery, while the control group guessed no better than chance would predict ($p < 0.004$). There are several possible reasons for this: for example, the suggestion group may have felt that their recovery was better than expected (as did the nurses) and guessed that they had heard an instruction tape, or the accuracy of their guesses may have been a direct result of registration without awareness during general anaesthesia. We did not set out to differentiate between these mechanisms.

Mackie correctly observes that the anaesthetist's experience was recorded for 18 of the 19 suggestion group patients. 1 patient was anaesthetised by a senior registrar.

Mackie accuses us of having "fallen into the trap of studying two things at once". He must be aware of the extensive work on psychological preparation for surgery.[1-3] Psychological interventions, especially those including the copying strategies which constituted three-quarters of our suggestion tape, may improve recovery from surgery. There are at least seven studies[4] that have evaluated psychological preparation for medical and surgical procedures done without general anaesthesia. All but one found a positive therapeutic effect.

Mackie has fallen into the trap of not differentiating between recall and registration of auditory stimuli during general anaesthesia. Recall of intraoperative events is almost invariably absent; but lack of verbal recall does not necessarily indicate lack of registration.[5] Furthermore, awareness is not necessary for registration to take place and information may affect later behaviour without that information being accessible to recall.[6] We cited neurophysiological, cognitive, behavioural, and clinical studies which indicate that auditory information is registered during general anaesthesia and that it may affect postoperative behaviour.

The study that Dr Mackie mistakenly cites is a good example of this: Bennett et al found that 9 of 11 patients responded postoperatively to instructions made during surgery despite complete amnesia for the precipitating instructions. These findings are not consistent with Mackie's conclusion: recall may be a rare occurrence but registration appears to be common and of considerable clinical importance.

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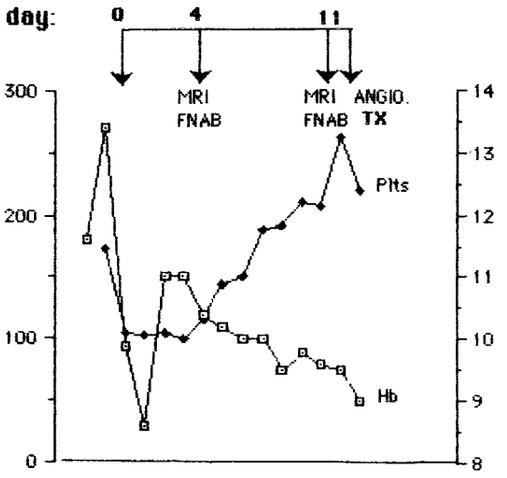
EARLY THROMBOSIS IN KIDNEY GRAFTED INTO PATIENT TREATED WITH ERYTHROPOIETIN

SIR,—Thrombotic side-effects such as vascular access thrombosis, convulsions, or clotting in the artificial kidney have been well described in haemodialysis patients treated with recombinant human erythropoietin (rhEPO) but we can find no information on the risk when the patient is transplanted. A 31-year-old patient who had been on haemodialysis for hypocomplementaemic glomerulonephritis since 1984 had an early graft thrombosis after renal transplantation.

This patient did not develop immunisation after transfusions. She was given rhEPO (Ortho-Cilag) 50 IU/kg three times a week from April, 1988. The haematological response reached a plateau at a haemoglobin of 11·9 g/dl; there were no side-effects such as hypertension or thrombosis. The last EPO infusion was given 24 hours before transplantation, after the last dialysis.

Transplantation (July 17, 24 hours cold ischaemia) was with a kidney from a women aged 45 who had died from a cerebral haemorrhage. The anastomosis of the iliac vessels was end-to-side. Immunosuppression was with antilymphocyte globulin 5 ml/kg, azathioprine 3 mg/kg, and methylprednisolone 10 mg/kg (rapidly tapered to 0·2 mg/kg) all daily. Post transplantation there was poor urine output (residual diuresis 1000 ml per day) and dialysis had to be continued. Aspiration biopsy yielded brown aseptic liquid but ultrasound examinations did not suggest gross haematoma.



Post-transplant course.

□ = haemoglobin (g/dl); ◆ = platelets (× 10^9/l).
MRI = magnetic resonance imaging; FNAB = fine needle aspiration biopsy; TX = removal of graft.

A magnetic resonance scan[1] of the graft on day 4 was normal but hyperdense images were seen on day 11, suggesting parenchymatous haemorrhage. Angiogaphy on day 12 confirmed total thrombosis of the renal artery, and this was followed by immediate removal of the graft. The graft showed diffuse thrombosis of all vessels and disseminated ischaemic necrosis. The precise timing of this early thrombosis is uncertain, but its development is very puzzling because there was no surgical complication, no perioperative hypotension, and no evidence of rejection (negative anti-HLA antibody titre, negative cross-match). So we are faced with the possibility that EPO and the high preoperative haematocrit were responsible.[2,3] However, the erythrocyte count fell to 60% of the initial value in the postoperative period, and platelet count has been persistently normal (figure). This isolated case does not prove a causal relation between EPO and graft failure and more information on the risk of thrombosis with EPO is needed. To exclude potential transplant recipients from the benefits of EPO would be a backward step in the management of uraemic patients.

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IS CYCLOSPORIN TOXIC TO ENDOTHELIAL CELLS?

SIR,—Cyclosporin controls the rejection of transplanted organs and its use is now expanding to other clinical areas. In ophthalmology cyclosporin is a new treatment for several inflammatory diseases. During therapy with cyclosporin for severe sight-threatening intermediate and posterior uveitis, 2 of 27 patients showed a bleeding tendency.

Case 1 (F 31, bilateral steroid-resistant intermediate uveitis complicated by macular oedema).—The starting dose of cyclosporin was 10 mg/kg per day and prednisone was gradually tapered to zero from 10 mg per day. Initially whole blood levels of cyclosporin twice peaked to high values (870 and 1120 ng/ml) and during this period the patient had recurrent epistaxis and menorrhagia. No systemic diseases were found and indices of coagulation were normal. Ocular inflammatory signs gradually disappeared and vision improved. After reduction of cyclosporin dose the bleeding tendency stopped and the uveitis remained stable. Withdrawal of cyclosporin therapy resulted in prompt recurrence of uveitis. For the past 16 months her uveitis has been well controlled by a low dose of cyclosporin (blood levels 200–300 ng/ml).

Case 2 (M 51, treated with high-dose prednisone for severe bilateral intermediate uveitis).—This patient had a short period of having multiple floaters in both eyes, caused by a small vitreous bleeding. Neovascularisation of the inferior peripheral retina was suspected. The patient was successfully treated for hypertension with enalapril 5 mg, triamterene 50 mg, and hydrochlorothiazide 25 mg daily. 6 months later daily oral cyclosporin (10 mg/kg) was started because steroid response was unsatisfactory. Within 48 hours both eyes showed massive vitreous haemorrhage and for almost 4 months vision of both eyes was severely reduced. Despite reduction of cyclosporin dose, blood levels twice reached high peaks (1490 and 1630 ng/ml). Pars plana vitrectomy of the right eye and cryocoagulation of the presumed retinal neovascularisation of the left eye did not prevent recurrence of vitreous bleeding in both eyes. Renal function showed minimum decline and blood pressure gradually increased. Coagulation tests were normal. After 4 months