company should produce a car of perfection; such perfection is also expected of Japanese doctors; this may prolong operations. British procedures, both surgical and anaesthetic, are quick and flexible but sometimes, I feel, rather less refined. Sterile techniques are often less thorough. To my surprise, spontaneous ventilation can be maintained with high-dose opioids and, to my astonishment, little happens, despite an increased measured end-tidal carbon dioxide concentration. In addition, the duration of hospital stay after surgery in Britain is usually shorter than that in Japan. I cannot but wonder if the tissue itself of British patients has more powerful healing abilities!

Morphine is used widely for postoperative pain relief in Japan. However, the required dose for weight is relatively small, and if we wished to change according to the British standards procedure, I would feel sure that I would find a greater incidence of respiratory depression in Japanese patients. Sadly, I have no objective data to support this observation. Nevertheless, some British anaesthetists agreed with my observation and admit that they would give reduced doses to Oriental patients. It may be interesting study the difference between the races.

In both countries, nowadays, the young seem not to be keen on religion. However, Christianity is as rooted in British feelings as Buddhism, Confucianism or Shinto in Japan, and expressed by rather dry and rational feelings in the U.K., but more emotionally in Japan. These differences make organ transplantation from brain-dead patients possible in the U.K. In Japan, brain death has not yet been accepted legally. Although more than 30 liver transplantations have been performed, all have been from living donors (except for one occasion when an imported liver from a brain-dead donor was used). The first heart transplantation was carried out in 1968, and the recipient lived for 83 days. However, the surgery fell under suspicion of overriding the donor and a second attempt has not yet been made.

In conclusion, I would like to express my gratitude again to all the colleagues I have met in the U.K. for their help. Every experience gave me opportunities to reassess my views. The Japanese anaesthetists and surgeons in Japan; it is a problem for us to demonstrate the fruits of our efforts to the world. I hope that we shall be able to use this visiting programme as a significant bridge between our countries.

A. Mizushima

Tokyo

ASPIRIN, EXTRADURAL ANAESTHESIA AND THE MRC COLLABORATIVE LOW-DOSE ASPIRIN STUDY IN PREGNANCY (CLASP)

Sir,—An editorial by Dr Macdonald [1] discussed the potential risk of extradural haematoma after extradural block in patients taking aspirin, and suggested that women taking aspirin during pregnancy should stop 7–10 days before delivery and have a bleeding time performed before extradural block is undertaken.

Even with small doses of aspirin (60 mg daily) the bleeding time may be prolonged because aspirin irreversibly inhibits cyclo-oxygenase in platelets [2]. A large multicentre randomised placebo-controlled trial (CLASP) [3] of the effects of aspirin 60 mg daily on the incidence of pre-eclampsia and its sequelae currently is being conducted, under the auspices of the Medical Research Council, in more than 200 hospitals in Britain and elsewhere. More than 7000 women already had been included in this study, and so far post-delivery data are available for more than 5000 women. The co-ordinators and collaborators remain blinded to the interim results, but a data monitoring committee (chaired by Professor Sir Richard Doll) reviews the unblinded data regularly. In view of the concerns that have been raised about extradural anaesthesia, these were reviewed in detail last year, and the data monitoring committee reported that: "The present position is that 1000 women are known to have had epidurals by the end of January 1991. Fifty-six adverse reactions, in the broadest sense of the term, have been reported in relation to epidurals, 26 in women on aspirin and 30 in women on placebo. Haemorrhage has been reported on three occasions, in all instances limited to blood-stained fluid in the cannula during treatment. One was in a woman on aspirin and two were in women on placebo. None of the other adverse reactions reported appear likely to have been due to haemorrhage. Aspirin had been stopped 23 days before delivery in the one case on aspirin, and placebo had been stopped 23 days before delivery and an unknown time before delivery in the other two cases". After a subsequent review in November 1991, it was reported that no further extradural bleeding had been recorded after an additional 592 extradural insertions. Review of data from the large Collaborative Perinatal Project [Brent, personal communication] indicates that, among 2269 mothers exposed to aspirin in the last 10 days of pregnancy, there was slightly, although not significantly, less bleeding than among 7606 unexposed mothers.

Dr J. D. Redman and Prof. Sir Richard Doll; in view of the concerns that have been raised about the risk of extradural haematoma after extradural block in patients taking aspirin during pregnancy, we urge that aspirin (or matching placebo) tablets be stopped at about 37 weeks gestation, at which time any beneficial effects of aspirin on pre-eclampsia or intrauterine growth retardation are likely to have occurred. We do not recommend that bleeding times are performed routinely in women who may have taken aspirin just before a planned extradural (as this is difficult to perform correctly and so may be misleading). It is felt that withholding extradural anaesthesia should be considered only if a conventional clotting screen performed for reasons other than possible aspirin use was abnormal (as patients in whom extradural anaesthesia is considered the technique of choice should not be denied it because of a remote, unconfirmed and probably remote, risk of extradural haematoma formation).

Case reports, such as the one cited by Macdonald [1], do provide reliable information about the incidence of any serious risks of aspirin use with extradural anaesthesia, and they do not provide anything more than an association (not a causal link) between aspirin use and bleeding in extradural anaesthesia. Reliable information about the size of any real risks is likely to emerge only from controlled studies, such as CLASP. In the meantime, we hope that the approach adopted for the trial may provide some balanced guidelines for anaesthetists faced with the likely growing use of aspirin in pregnancy.

M. de Swiet

Co-Chairman, MRC Working Party for CLASP


Sir,—Thank you for the opportunity to read this letter from Drs de Swiet and Redman. In their letter they state quite rightly that the bleeding time may be prolonged even with low doses of aspirin (60 mg daily). Consequently, all patients in the CLASP trial who have ingested aspirin are likely to have a prolonged bleeding time. The obstetric anaesthetists' anxiety concerning the sitting of an extradural block in a patient who has ingested a low dose of aspirin is not that there will be an increased incidence of vessel puncture, but that, should such a puncture occur, then bleeding into the extradural space will be prolonged as a result of the ingestion of the aspirin. What we do not know is how much bleeding will occur in relation to prolongation of the bleeding time. Will the volume of blood released into the extradural space from a vessel puncture be sufficient to cause a clinically significant extradural haematoma?

I reiterate that the best test of platelet function after aspirin ingestion is estimation of the bleeding time. This is more relevant than a full clotting screen. I suggest that, with attention to detail, a bleeding time can be performed reliably and reproducible results achieved.

Nevertheless, in view of the fact that patients in CLASP are ceasing aspirin ingestion at about 37 weeks, it would appear that...
problems from this study are not going to be as great as was originally anticipated.

I return to my basic thesis that any patient on routine aspirin or NSAID medication [1] should have a bleeding time performed before an extradural is sited. If the bleeding time is prolonged beyond 10 min, then the anaesthetist must balance the advantages and disadvantages of siting the extradural in that particular patient.

R. MACDONALD
Leeds


ATRACURIUM AND HISTAMINE

Sir,—I was interested to read the paper by Adt, Baumert and Reimann on the role of histamine in the cardiovascular effects of atracurium [1], in which work by myself and colleagues was quoted extensively [2, 3]. I would like to congratulate them on a well executed and researched project. The obvious question is, of course, how much one may infer about the true haemodynamic side effects of a drug when patients recruited to the study have been prescribed preoperative cardiovascular medications? These drugs may well obtrude or exaggerate any haemodynamic event after i.v. administration of a large bolus dose of atracurium. I think the authors need to look in more detail at the individual patient responses and the preoperative medication. It is interesting, however, to observe the data on cardiac index and systemic vascular resistance.

R. P. F. SCOTT
Salisbury


Sir,—Thank you for the opportunity of replying to Dr Scott’s comments. Conditions for clinical studies are optimal when healthy individuals are investigated and all interfering medication is excluded. We represent a clinic for cardiac disease where all patients undergoing surgery. She was not currently receiving medication and did not contain only vecuronium, ruling out the possibility that the patient received any other drug other than that stipulated.

In an effort to confirm the finding, the patient agreed to donate blood for an in vitro experiment. A solution of vecuronium 2–2.5 μg ml⁻¹ was added to the patient’s plasma and 2 ml samples

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PROBABLE RESISTANCE TO VECURONIUM INVOLVING THE 17-HYDROXY METABOLITE

Sir,—The editorial by Hunter [1] has prompted this report of a case of probable resistance to vecuronium accompanied by the detection of its 17-hydroxy metabolite. A 26-year-old worker (weight 62 kg), being otherwise healthy, was to undergo knee surgery. She was not currently receiving medication and did not undergo knee surgery. She was not currently receiving medication and did not abuse alcohol or other chemical substances. Premedication comprised diazepam 10 mg orally and pethidine 50 mg i.m. After administration of glycopyrrolate 0.2 mg and vecuronium 1 mg, anaesthesia was induced i.v. with thiopentone 250 mg and the trachea was intubated with the aid of suxamethonium 100 mg. The patient’s lungs were then ventilated manually with nitrous oxide and 1% endotrace in oxygen. Vecuronium 4 mg was injected, but without effect: the peripheral neuromuscular block showed no fade on train-of-four stimulation. A new ampoule of vecuronium, of the same batch, was prepared and a second 4-mg dose of the drug was administered again against no demonstrable neuromuscular block. As the patient was coughing on the tracheal tube, thiopentone 100 mg was given i.v. Venous blood samples were taken (which were sent to the laboratory for centrifugation and then stored at −70 °C). The patient then received pancuronium 3 mg which provided neuromuscular block sufficient for the 45-min surgery. The residual block was antagonized with neostigmine-glycopyrrolate and the postoperative course was uneventful.

The blood samples, and ampoules of vecuronium belonging to the same batch as that given, were analysed at the University Hospital, Groningen. The serum and plasma samples, respectively, contained 17-hydroxy vecuronium 304 and 305 ng ml⁻¹ and vecuronium 35 and 65 ng ml⁻¹. The ampoules were found to contain only vecuronium and ruling out the possibility that the patient received any other drug other than that stipulated.

In an effort to confirm the finding, the patient agreed to donate blood for an in vitro experiment. A solution of vecuronium 2–2.5 μg ml⁻¹ was added to the patient’s plasma and 2 ml samples