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 I were to take some anaesthetists' word for it, I might feel 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 is in the Chinese and 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 surgeon fell under suspicion of ordering the donor and a second attempt has not yet been made.

In conclusion, I would like to express my gratitude again to all of the colleagues I have met in the U.K. for their help. Every experience gave me opportunities to reassess my views. The Japanese are often said to be different from the other Japanese; 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. All patients in the CLASP trial who have ingested aspirin are likely to have a prolonged bleeding time. 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 randomized 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 injections. Review of catheter tip blood samples taken after delivery in both the aspirin and control groups (60 mg daily) the bleeding time was longer than a full clotting screen. I suggest that, with attention to detail, a bleeding time can be performed reliably and reproducible results achieved.

Correspondence

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 from extradural space will be prolonged after a low dose of aspirin. In their case report they state that blood from vessels 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 sited 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 can infer about the true haemodynamic side effects of a drug when patients recruited to the study have been prescreened for preoperative cardiovascular medications? These drugs may well blunt 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 had received premedication before enrolment and we are especially interested in obtaining data from these patients. However, while there is compelling evidence (see below) that such patients react sensitively to intraoperative histamine release, effective intraoperative protection can be achieved by means of H1- and H2-receptor antagonists.

We have shown that a transient increase in plasma histamine concentration occurs after i.v. heparin, which could account for a cardiovascular reaction \[1, 2\]. In differing patients, different plasma histamine concentrations can occur, for which different preoperative medications may be partly responsible. However, there is no clear relationship between medication and cardiovascular reaction pattern; for example, patients with and without beta receptor blockers did not develop tachycardia, and the decrease in mean arterial pressure after histamine release was independent of antihypertensive premedication. Lorenz and Doenicke have demonstrated that, in approximately 3% of all patients undergoing surgery, serious to life-threatening plasma histamine concentrations occur—for example after administration of antibiotics—whereas the incidence of all types of histamine reactions may be as great as 20–30%. We believe that the variety of drugs administered during surgery is the cause of in calculable histamine release and that preoperative medication is of lesser importance for cardiovascular sequelae.

During coronary artery surgery there is a tendency to interpret intraoperative arrhythmias as cardiac ischaemia. However, Levi's group have achieved very impressive results in animal studies, showing that cardiac anaphylaxis is an independent pathological phenomenon in which histamine often plays a lethal role \[4, 5\]. Similarly, preliminary results of an in vitro study of mast cells from human hearts show that these mast cells do, in fact, release histamine when perfused with drugs that are clinically suspected to be histamine liberators. These results underline that the influence of histamine on the heart is of a clinical importance which has yet not been completely investigated.

It is our philosophy to protect patients with a deficient cardiovascular system against histamine-mediated reactions, occurring during anaesthesia, by means of prophylactic administration of H1- and H2-receptor antagonists. The aim of the study under discussion was, first, to establish the amount of histamine released and the cardiovascular reaction induced by a clinical dose of atracurium and, second, to investigate if muscle relaxants in these patients can be achieved safely following the above-mentioned "prophylaxis". In our opinion, both questions have been answered adequately.

M. Adt
Berlin


**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-yr-old waitress (weight 62 kg), being otherwise healthy, was to undergo knee surgery. She was not currently receiving medication and did not abuse alcohol or other chemical substances. Premedication comprised diazepam 5 mg orally and pethidine 50 mg i.m. After administration of glycopyrronium 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% enflurane in oxygen. Vecuronium 4 mg was injected, but without effect: the peripheral neurostimulator showed no fade on train-of-four stimulation. A new ampoule of vecuronium was prepared and a second 4-mg dose of the drug was administered, again with no demonstrable neuromuscular block. As the patient was coughing on the tracheal tube, thiopentone 100 mg was given i.v. Ventous 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-glycopyrronium 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 have contained vecuronium 35 and 65 ng ml−1.

During coronary artery surgery there is a tendency to interpret intraoperative arrhythmias as cardiac ischaemia. However, Levi's group have achieved very impressive results in animal studies, showing that cardiac anaphylaxis is an independent pathological phenomenon in which histamine often plays a lethal role \[4, 5\]. Similarly, preliminary results of an in vitro study of mast cells from human hearts show that these mast cells do, in fact, release histamine when perfused with drugs that are clinically suspected to be histamine liberators. These results underline that the influence of histamine on the heart is of a clinical importance which has yet not been completely investigated.

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