Placebo trials: a time for change?

Editor,—In the recent editorial on ethical review of research, it is stated clearly that ‘Placebos may be used as comparators only in studies of conditions for which there is no known treatment with which the trial drug could be compared’. 1 This poses a dilemma for the editors. First, the journal could continue to publish articles of placebo studies contrary to its own editorial. Second, the journal could act on its own recommendation and apply these ethical standards to future articles submitted. Rejecting an article on ethical grounds, where the study has been accepted by a Local Ethics Committee, is suggesting that one ethical opinion is superior to another and may cause offence, especially in the context of cultural differences. However, if a study is rejected by British Ethics Committees then it is equally unethical to publish the same study performed elsewhere. In these cases, perhaps it should be suggested that publication is sought in the authors’ regional journal. In the longer term, authors would accept new standards and alter studies accordingly.

This abrupt change in ethical standards has precedents. Placebo groups in antiemetic studies have all but disappeared from oncology studies following editorial criticism2 whereas they appear regularly in anaesthesia studies. Gilbertson’s editorial has given this journal the opportunity to raise ethical standards concerning placebo usage and should be eagerly seized as an example for others to follow.

J. P. Clarke
Department of Anaesthesia
Flinders Medical Centre
Adelaide, Australia


Editor,—Thank you for the opportunity to reply to Dr Clarke’s letter. May I first comment on the use of placebo in clinical studies and then on the publication of unethical research.

My authority for stating that it is not ethical to include a placebo arm in a clinical study in a condition for which an effective treatment exists, and with which the study drug could be compared is, inter alia, the latest revision of the Declaration of Helsinki, to which I referred. 1 Paragraph II (3) states ‘In any medical study, every patient—including those of a control group, if any—should be assured of the best proven diagnostic and therapeutic method. This does not exclude the use of an inert placebo in studies where there is no proven diagnostic or therapeutic method exists’. It is apparently assumed that there is good reason to expect that the drug or method under investigation will be at least as effective as the best previously proven diagnostic or therapeutic method.

This document is published by the World Medical Association to which 63 national medical societies are affiliated. I had until this week thought that the British Journal of Anaesthesia should adhere to this ethical standard, regardless of the country of origin of the research. However, an article in the British Medical Journal2 caused me to think again. The article refers to a study in Thailand which showed that oral zidovudine given in late pregnancy and labour to non-breast feeding mothers reduced the rate of mother to child transmission of HIV by 51% (95% confidence interval 15–71%). Within days of the release of these data, investigators studying other regimens closed recruiting to the placebo arms of their studies (because an effective treatment, zidovudine, had now been shown to exist) and it is unlikely that funding would be made available for further placebo-controlled studies of interventions aimed at reducing maternal transmission of HIV. However, the authors of the BMJ article point out that the Thai study is not relevant to conditions in many parts of Africa, and that oral zidovudine is simply not affordable in many African regions. Although an effective treatment exists, in practice it does not exist, and will not exist in those regions in the foreseeable future. Cheaper treatments which may be affordable and which would be less effective than zidovudine but more effective than a placebo could ethically be tested against a placebo in that region, because the research subjects could not receive effective treatment outside the study. No one would suffer from the trial and some might benefit and it would not be unethical to publish the results. The wording in the next edition of the Declaration of Helsinki should perhaps be changed to ‘This does not exclude the use of an inert placebo in studies where no proven diagnostic or therapeutic method exists or where none is available’.

Dr Clarke’s letter refers to the dilemma facing editors of medical journals; is it unethical to publish studies which would be judged unethical by a British Research Ethics Committee? If researchers knew in advance that no reputable journal would publish the results of unethical studies, they would be encouraged to ensure that the protocol was ethical by international standards. On the other hand, it might be argued that if editors refuse to publish useful results of unethical studies, patients may suffer as a result of their doctors’ ignorance of information which could have been made available. A considerable proportion of the knowledge—
base of modern medicine has been obtained from research which would not now be permitted. Should not the harm to patients which would result from refusing to publish such information be balanced against the likelihood that unethical research would be discouraged if the researchers knew that it is unlikely that they could find a publisher.

There are some things we simply do not have the authority to do, even to achieve a result which is in itself good. We do not have the authority to encourage harm to research subjects, even though the object would be to alleviate the suffering of patients. The last sentence in the Declaration of Helsinki is ‘In research on man, the interest of science and society must never take precedence over considerations related to the well-being of the subject’. The policy of the British Journal of Anaesthesia and other reputable journals should be to publish only ethical research: the use of placebos where an effective treatment exists and is available jeopardizes the well-being of the subject and is not ethical. I agree with Dr Clarke that such studies should not be published.

A. A. Gilbertson
Chairman, Liverpool Local Research Ethics Committee
Liverpool, UK

2 Wilkinson D, Abdool Karim SS, Coovadia HM. Short course antiretroviral regimens to reduce maternal transmission of HIV. BMJ 1999; 318: 479–80

Propofol and epilepsy

Editor,—I am surprised at the requirement for an editorial on propofol and epilepsy. There is no new evidence to suggest that propofol causes epileptiform activity, as defined by EEG analysis. The nearest evidence clearly states the sub-anaesthetic doses used to provoke such EEG changes, in the same manner as with thiopental. Thus far only the onset of slow wave (delta) activity has been recorded, with onset of slow wave (delta) activity has been recorded, with a few patients showing dystonic reactions to propofol.

Indeed, in our own series now numbering 52, of patients undergoing ‘awake’ resections of dominant hemisphere epileptic foci under target-controlled infusions of propofol, we have had only two patients who did not recover from infusion, to allow accurate functional mapping, in less than 11 min. We suspect that these two patients may have suffered a complex partial seizure during the craniotomy phase but have no evidence to support this. Indeed, their outcome was no different from the rest of the group.

To quote an anonymous reference from a Data Sheet Compendium to support the argument for the conclusion that propofol should probably be avoided in epileptics with a driving licence is a little over zealous. The addition of the word ‘probably’ emphasizes the uncertainty of the conclusion.

Until such time as clear scientific evidence points to the propagation of convulsive EEG changes associated with dystonic movements on administration of inductive doses of propofol to patients, at appropriate rates, then propofol can be administered safely to epileptic patients. After all, there were a number of case reports in peer-reviewed journals of propofol infusion being used to control refractory status epilepticus in 1987–8. This is fact, not fiction.

N. J. Huggins
Featherstone Department of Anaesthesiology
Queen Elizabeth Hospital
Edgbaston, Birmingham, UK


Editor,—I am grateful to Dr Huggins for his interest in my editorial. Propofol has been associated repeatedly with a range of excitatory events and sedative doses produced unequivocal increases in epileptiform activity in a proportion of patients during recordings from electrodes within or on the surface of the human brain. Clinical experience has shown propofol to be an effective anticonvulsant in animals and humans. All of these points were clearly made in the editorial.

The key point overlooked by Dr Huggins is that epileptic patients will lose their driving licences as a consequence of any excitatory episode, including myoclonus and opisthotonus, regardless of the state of the EEG at the time. Therefore, it remains appropriate that clinicians should be guided by pragmatism in addition to science and not use this agent in epileptics who hold a current driving licence or have a reasonable prospect of doing so. To insist that propofol ‘can be administered safely to epileptic patients’ until there is evidence that convulsive EEG changes with dystonic movements can be demonstrated after induction doses of propofol, is a council of scientific perfection. An epileptic motorist who lost his licence as a consequence of such dogmatism would probably not appreciate the subtleties of this argument.

I stand by my recommendation that ‘in other epileptics and in status epilepticus, its use can easily be justified.’

J. R. Sneyd
Department of Anaesthesia
Derriford Hospital
Plymouth, UK
Editor,—Myocardial perforation is a rare complication of pulmonary artery catheterization. We describe a case of perforation of the right ventricle caused by a pulmonary artery catheter during coronary artery bypass surgery. A 71-yr-old man with three-vessel coronary artery disease and unstable angina pectoris was considered for coronary artery bypass surgery. Coronary angiography revealed total occlusion of the left anterior descending artery and the right coronary artery, and partial occlusion of the left circumflex artery. Left ventriculography showed no segmental wall motion dysfunction or aneurysm. Ejection fraction was within normal limits (0.61). There were no electrical or laboratory signs of myocardial infarction.

After induction of anaesthesia and tracheal intubation, a pulmonary artery catheter (7.5 FR VIP, Baxter, Irvine, CA, USA) was inserted via a percutaneous sheath introducer (8.5 FR, Arrow, Reading, PA) placed in the right internal jugular vein. The catheter was advanced to the 20 cm mark. The balloon was then inflated with 1 ml of air. Despite multiple attempts, the tip of the catheter could not be passed from the right ventricle into the pulmonary artery. The balloon was then deflated and the tip of the catheter was left in the right ventricle. There were no arrhythmias or haemodynamic disturbances during the catheterization attempts. The chest was opened with a median sternotomy incision. After opening the pericardium, the tip of the pulmonary artery catheter was seen protruding through the inferior wall of the right ventricle. The catheter was withdrawn into the right atrium, and the perforation was closed with 3/0 sutures on pledgets; the patient subsequently underwent coronary artery bypass surgery. Recovery was uneventful and the patient was discharged 10 days after surgery with no residual complications.

Factors that predispose to ventricular perforation during catheterization include small chamber size, a stiff catheter, outflow tract obstruction and myocardial infarction.1 There was no evidence of pre-existing right ventricular weakness in our patient and perforation was most likely caused by a stiff catheter. The perforation potential of pulmonary artery catheters is increased by cooling and by the presence of multiple lumens.2,3

Right ventricular perforation is a hazard of using the pulmonary artery catheter if the uninflated tip remains in the ventricle. Haemopericardium can occur unless the pericardium is opened. A catheter left in the right ventricle may also cause arrhythmia after cardiac surgery. Withdrawing the catheter to the right atrium will prevent this complication.

D. Karakaya
S. Baris
A. Tür
Ondokuz Mayas University
Faculty of Medicine
Department of Anaesthesiology
Samsun, Turkey

Remifentanil and rapid sequence induction

Editor,—I read with interest the short communications on remifentanil and rapid sequence induction.1,2 As stated by the authors, ‘rapid sequence induction is often associated with significant haemodynamic changes which are potentially harmful’.2 The indication for performing rapid sequence induction is to obtain a secure airway with a cuffed tracheal tube, as quickly as possible, when there is a risk of regurgitation and aspiration. This necessitates the use of an induction agent and rapidly acting neuromuscular blocker (usually succinylcholine) given in rapid succession.

In this study, thiopental was given and cricoid pressure applied as consciousness was being lost. The study drug was then given as a bolus of 15 ml over 30 s, followed by succinylcholine, which was allowed another 60 s to take effect before laryngoscopy and intubation. Administration of remifentanil between thiopental and succinylcholine compromises rapid sequence induction and may increase the risk of regurgitation and aspiration.
Many of the patients who potentially suffer harmful side effects from rapid sequence induction are the middle-aged in whom there is a high incidence of asymptomatic heart disease, and the elderly, many of whom are receiving treatment for cardiovascular problems. The latter are in the age group who most commonly undergo urgent surgery, for example intestinal obstruction, and are at very high risk of aspiration. They are also the group in whom attenuation of the sympathetic response to intubation is most desirable. As the authors excluded patients receiving drugs with cardiovascular effects, no conclusions can be drawn from this study on these patients.

Other short-acting opioids and i.v. lidocaine have been used with varying amounts of success. Although remifentanil generally prevented the pressor response after intubation in this study, one has to balance this benefit against the possible increased risk of aspiration using this modified form of rapid sequence induction.

N. R. K. Anders
Department of Anaesthesia
Royal Manchester Children's Hospital
Pendlebury, Salford, UK


Editor,—Thank you for the opportunity to respond to Dr Anders’ comments. While it is true that induction should proceed rapidly during rapid sequence induction, there was a delay of only approximately 30 s in this process in our study. However, patients’ lungs were preoxygenated, cricoid pressure was maintained throughout, and bag and mask ventilation was not carried out during this time. Therefore, there is very little likelihood of any desaturation and indeed none was observed in any patient in our study. Hence we do not consider this short period of time as a risk factor.

We have not drawn any conclusions about the effectiveness or side effects of remifentanil in patients with cardiovascular disease as no such patients were studied. However, when any new technique is tried, it is important to establish its safety and effectiveness in patients who are not at risk. A study in the type of patients highlighted by Dr Anders would be indicated to assess the benefits and any possible drawbacks of using remifentanil, having first established its safety in otherwise healthy patients.

R. O’Hare
D. McAtamney
R. K. Mirakhur
D. Hughes
U. Carabine
Department of Anaesthetics
The Queen’s University of Belfast, Belfast, UK

This is one of the latest volumes in the Problems in Anaesthesia series. It consists of 11 chapters contributed by various authors (including the editor), all of whom are anaesthetists working in the USA. The first chapter is on latex allergy and while not specific to children, presents a good review and bibliography of the subject which could be usefully read by anaesthetists, surgeons and nurses. The second chapter covers anaesthesia outside the operating theatre and consists of a discussion of some of the applications and techniques. Diagnostic radiology receives most attention but the British reader will find the paragraph on dental anaesthesia remarkably brief.

The chapter on the management of the difficult airway begins with a succinct summary of the problem, in particular the lack of standard equipment and dangers of sedation of the otherwise uncooperative child; its subsequent discussion of the ‘lightwand’ is sadly let down by the accompanying photographs which fail to demonstrate the light illuminating the soft tissues of the neck. Brief mention is made of the laryngeal mask, and the use of the cuffed oropharyngeal airway is presented in some detail although without any reference to the difficult airway. The chapter on preoperative preparation and premedication cites 14 of the author’s own publications but does not offer any practical help to the anaesthetist.

An excellent chapter on apnoea syndromes is, in my opinion, the highlight of the book. Written by Galinkin and Kurth from Philadelphia, it reviews the pathology, presentation and management of apnoea from prematurity to childhood. Clear, concise reviews of sudden infant death syndrome, postoperative apnoea in early life, obstructive sleep apnoea in the older child and Ondine's curse are accompanied by a useful, contemporary bibliography. The chapter on regional anaesthesia summarizes some techniques but does not really add to the published work already available. The chapter on postoperative problems dwells in particular on vomiting and offers some suggestions for its management, with a particular bias towards cost effectiveness. The British reader will find consideration of treatment in terms of dollars per patient kilogram to be novel. It is accompanied by a summary of the pharmacology of antiemetic drugs.

Only 10 of the 62 cited references in the chapter on halogenated inhalation agents are dated later than 1995, making one wonder just how topical this subject is. The chapter on cancelling surgery starts well with some common sense guidelines on upper respiratory tract infections and asthma, but then seems to lose its way as it drifts from cardiac murmurs to prematurity to fasting to cervical spine instability.

The final two chapters examine the management of pain in children. The chapter on cancer pain is authoritatively written with some useful suggestions in terms of philosophy, overall management and drug doses. The chapter on acute pain reviews the pharmacology and efficacy of systemic and local analgesia with a particularly useful review of continuous epidural analgesia containing practical advice and suggested drug doses.

In summary, this is not a textbook of paediatric anaesthesia for the trainee, neither is it a comprehensive reference book for the practising paediatric anaesthetist. However, it does cover many of the aspects of modern paediatric anaesthetic practice and could be useful in the stimulation of discussion and debate within departments of anaesthesia.

I. Barker


This is a timely, educational and challenging book: timely because ‘central’ pain afflicts a significant number of individuals, and educational because the author has reviewed the subject extensively (approximately 900 references). Clearly, the book is expected to be challenging to the neurosurgeon. However, I believe that it will stimulate and challenge others (such as those involved in the management of chronic pain) to consider afresh the underlying mechanism of ‘central’ pain and, maybe more importantly, to consider different modalities of management.

Any understanding of this monograph depends largely on two factors: first, an appreciation of the background of the author and second, his definition of ‘central’ pain. Professor Carlo Alberto Pagni is Professor of Neurosurgery in the University of Turin, Italy. He has published extensively in the field of chronic pain and has contributed to many of the standard texts, particularly from a neurosurgical perspective. In fact, the present monograph is a compilation of much of his own work and that of his co-workers, which has been set in the context of the work of others.

The IASP defines central pain as ‘pain initiated or caused by a primary lesion or dysfunction of the central
nervous system’. It has been described as a ‘diffuse, unilateral pain, often burning with allodynia, hypoalgesia, neurologically associated signs of damage to structures which supply the affected region’. The structures involved are the cerebral hemispheres, brain stem and spinal cord. Pain attributable to damage of peripheral nerves is not included. This is an important distinction not only for the readers of this monograph but also from a clinical perspective. There has been a tendency to associate pain caused by injury or disease of peripheral nerves with that caused by disease or injury to the central neuraxis under the term of ‘deafferentation’ pain. Professor Paggi argues against this tendency, highlighting the fact that, in his opinion, central pain can be caused by ‘any lesion of the nervous system, of any aetiology, that affects, either completely, incompletely or subclinically, the spinothalamocortical pathway, at any level, including the cortex’.

Personally, the most educational part of the monograph was chapter 4, ‘Survey of lesions causing central pain’. The author divided these into ‘spontaneous lesions’ and ‘iatrogenic lesions’. With regard to the former, he pointed out that pain caused by lesions in the thalamus was not the most frequent type of central pain, arguing that probably about half of the ‘spontaneous’ lesions that cause central pain do not involve the thalamus. The author goes on to argue that many diseases/lesions (vascular, neoplastic, degenerative) of the central nervous system may result in central pain, be they in the cortex, thalamus, brain stem or spinal cord. Not surprisingly, perhaps, significant consideration is given to central pain associated with spinal cord injury: however, pain associated with stroke, syringomyelia, multiple sclerosis and spinal epilepsy, for example, receives due mention. The second part of chapter 4 reviews those surgical procedures which have, at one time or another, been used in an attempt to relieve pain. Unfortunately, many of these appeared to initiate rather than relieve the pain or led to an increase in severity (iatrogenic lesions). As a result of this review, the author believes that spontaneous or surgical lesions can trigger central pain provided the spinothalamic tract is damaged whatever the involved neurone (first, second, third) and that no central pain ever followed damage of the descending pain-suppressing fibres. However, central pain has many puzzling effects: in particular, why should the same type of lesion, in the same anatomical area of the central nervous system, produce intolerable pain in one patient and have no effect in another? In the following chapter the author attempts to draw together the various theories of central pain and tackles this subject logically and scientifically. Nevertheless, I believe that he would agree that he has failed to develop a ‘global doctrine of central pain’. In other words, no one theory can explain fully the idiosyncratic characteristics of central pain. Not surprisingly, therefore, the treatment of central pain is often unrewarding.

The treatment of central pain is reviewed in the next chapter. Much is given over to a review of neurosurgical techniques: pharmacological management is covered in approximately three pages and does not include consideration of the newer anticonvulsant drugs, such as lamotrigine or gabapentine, although these are mentioned en passant in the conclusion to the chapter. What is clear, unfortunately, is that central pain is not a homogeneous entity and that, as a result, management is somewhat ‘hit or miss’. Likewise, it seems unlikely that any breakthrough is just ‘around the corner’, although the advent of new drugs and/or the use of neural transplantation techniques may hold promise for the future.

This is an interesting and detailed review of a difficult subject. Although the neurosurgical perspective is prominent, there is much in the monograph to interest other clinicians who deal with patients suffering from chronic pain.

W. Fitch

Essentials of Cardiac and Thoracic Anaesthesia.

This is an excellent book, and a timely one. You should buy it if you are a trainee who has to pass examinations; if you are thinking of taking a professional interest in cardiac or thoracic anaesthesia; or if you are charged with creating subspecialty training programmes or appointing consultants to one or other or both.

For the examination candidate, the book reaches the expressed intention to be didactic and comprehensive. The chapter layout is easy to surf through to obtain a broad overview of the disciplines: many of the concepts are represented by schematic representations, some taken from the standard specialist texts. The additional reading advice is excellent and up-to-date; it is inexpensive and will serve as a reference book for many years to come.

Often I have said (tongue-in-cheek) that cardiac anaesthetists make terrible thoracic anaesthetists but thoracic anaesthetists make excellent cardiac anaesthetists, the latter a high wire act, the former doing their stunts at lower altitude and with a safety net of cardiopulmonary bypass. There is also a difference in fundamental philosophy: the cardiac anaesthetist is directed by a need to maintain, above all, blood flow, most notably through the coronary vessels whereas the thoracic anaesthetist has to keep a wary eye on preserving the alveolar–capillary membrane. The fact that performances are often in the same tent should really be an anachronism but the UK sticks doggedly to the concept that the same surgical
groupings should be doing both. It is difficult, given the political and medico-legal climate, to see for how much longer this can be maintained. This book clearly differentiates with its dedicated separate sections. The subspecialty trainee reader will get a feel for these aspects in addition to a ready-made, do-it-yourself guide to managing the technical aspects of the perioperative experience of most of those patients who with sickness have paid to see the performance. Although ‘grown up’ congenital heart disease is dealt with, the bulk of paediatric cardiac surgery is not, and equally, although acute pain relief is comprehensively dealt with, the chronic pain syndromes of sternotomy and thoracotomy are not addressed.

And now a polemic for that last group of purchasers! This book defines the breadth and width of the cardiac and thoracic anaesthesia crafts. From it can be seen the knowledge that needs to be garnered, and the amount of practical experience it is necessary for subspecialty trainees to acquire in order to become the safe and skilled practitioners the public requires. The training time necessary, please note, is not defined. No longer can the teaching, training or destiny of cardiac or thoracic anaesthesia be dictated by amateurs and well-meaning groupies in ivory towers. You too will realize when you read it, there is come an age for the service of a new public—it is professional.

I. D. Conacher


International Anesthesiology Clinics was first published in 1962 by Little, Brown and Company, Inc. The series is known worldwide, not just because it is a subscription series but because many of the quarterly volumes have been of great service to anaesthesia as a well informed resource. Dr Feeley, who has been Editor-in-Chief since 1993, has assembled this volume as a compendium of ‘classics’ from the period 1962 to 1970. The scope is confined to the physiology and pharmacology of clinical anaesthesia, and two practical chapters on paediatric anaesthesia from J. B. Stetson and Robert M. Smith, respectively, both published in August 1962. Other chapters that will be familiar to many include ‘Intercostal nerve block’ by Daniel C. Moore (1963), ‘Atrial activity and anaesthesia’ by Myron Laver (1963), and John Dundee’s introductory section on ‘Intravenous anaesthesia’ (1964).

‘Alveolar–arterial Po2 differences in anaesthesia’ by John Nunn (1966) is a well written piece, as might be expected, but does not represent all that the author had to say on this important topic to which he contributed so much. I recognize, however, that my idea of more definitive pieces cannot be found in International Anesthesiology Clinics. Incidentally, I was sorry to note that Dr Feeley described Professor Nunn as a Professor of Anaesthetics at Leeds. I happen to know that John Nunn insisted on the title of Anaesthesia but only after intensive relevant research!

I was a little surprised by Dr Feeley’s editorial note in relation to Michael Dykes’ chapter on hepatic dysfunction (1970). Dr Feeley states that by 1970 ‘the halothane hepatitis controversy was finally coming into perspective among anesthesiologists’. I do not fully comprehend Dr Feeley’s perspective in this matter but from my point of view the controversy was just warming up. In passing, I would comment that the anaesthetic community’s handling of the halothane controversy remains an outstanding example of the need for evidence-based medicine; it may also point to the need for greater integrity in ‘scientific’ communication in clinical matters.

Perhaps I could also comment on the chapter by C. V. Bergquist on diethyl ether (1963). Presumably it all depends on where one worked. But I commenced anaesthetic practice in 1961, understanding that diethyl ether had virtually no part to play in Scottish anaesthetic practice at that time. We did, of course, have the benefit of chloroform, and almost everyone struggled with trichloroethylene, and with cyclopropane, which is represented in this volume in a chapter by J. S. Denson. One wonders if Dr Feeley, in his editorial note for this chapter, was tempted to say that cyclopropane gave a degree of control of anaesthesia that has only been matched by sevoflurane.

I question if the practice of anaesthesia in the 1990s would derive very much from the perusal of the writings that are reproduced in this volume, and I would imagine that the book is of interest only to those of a certain age. In spite of that, the book is an elegant production, and I have derived entertainment and pleasure from reading it.

A. A. Spence