ANZ J. Surg. 2008; **78**: 540–547 doi: 10.1111/j.1445-2197.2008.04568.x

CLINICAL REVIEW

ANAESTHESIA AND ANALGESIA: CONTRIBUTION TO SURGERY, PRESENT AND FUTURE

EDWARD SHIPTON AND ANTHONY LIN

Department of Anaesthesia, Christchurch School of Medicine, University of Otago, Christchurch, New Zealand

Anaesthetists provide comprehensive perioperative medical care to patients undergoing surgical and diagnostic procedures, including postoperative intensive care when needed. They are involved in the management of perioperative acute pain as well as chronic pain. This manuscript considers some of the recent advances in modern anaesthesia and their contribution to surgery, from the basic mechanisms of action, to the delivery systems for general and regional anaesthesia, to the use of new drugs and new methods of monitoring. It assesses the resulting progress in acute and chronic pain services and looks at patient safety and risk management. It speculates on directions that may shape its future contributions to the management of the patient undergoing surgery.

Key words: anaesthesia, analgesia, contribution to surgery.

Abbreviations: AEP, auditory-evoked potentials; COX-2, cyclo-oxgenase 2; CSA, continuous spinal anaesthesia; CSE, combined spinal and epidural; EEG, electroencephalograph; $GABA_A$, gamma-aminobutyric acid-A; PONV, postoperative nausea and vomiting; TCI, target-controlled infusion; TOE, transoesophageal echocardiography.

INTRODUCTION

William Morton first publicly showed inhalational anaesthesia in 1846 with the use of diethyl ether. At the end of the nineteenth century, August Bier discovered that a class of drugs (local anaesthetics) could stop neural transmission. Since those humble beginnings, the application of anaesthesia and analgesia has advanced rapidly particularly in the past 50 years, making surgery much safer and allowing more sophisticated surgery to take place. The explosion hazard with anaesthetic gases was largely conquered with the development of the halogenated agents in the 1950s. Introduction of sevoflurane and desflurane during the last decades offered new perspectives to clinical anaesthesia, characterized by rapid onset of and recovery from anaesthesia.

Anaesthetists provide comprehensive perioperative medical care to patients undergoing surgical and diagnostic procedures, including postoperative intensive care when needed. They are involved in the management of perioperative acute pain as well as chronic pain. This manuscript considers some of the recent advances in modern anaesthesia and their contributions to the management of the surgical patient. They range from the 'basic mechanisms of action', the delivery systems for general and regional anaesthesia, the use of new drugs to the new methods of monitoring. The resulting progress in acute perioperative and chronic pain services is assessed in addition to patient safety and risk management. It speculates on directions that may shape any future contributions.

E. Shipton DM, FANZCA, FFPMANZCA; **A. Lin** MBChB.

Correspondence: Professor Edward Shipton, Department of Anaesthesia, Christchurch School of Medicine, University of Otago, PO Box 4345, Christchurch 8042, New Zealand.
Email: shiptonea@xtra.co.nz

Accepted for publication 15 October 2007.

MECHANISMS OF ACTION

How do anaesthetics work? Despite the widespread presence of clinical anaesthesiology in surgical practice, the mechanisms by which diverse inhalational agents give general anaesthesia remain unknown. There are complex multisite, multilevel (molecular, subcellular, cellular, local microcircuit) interactions.[1] Binding sites for general anaesthetics have been identified on several ion channels, including the nicotinic acetylcholine and gamma-aminobutyric acid-A ($GABA_A$) receptors.[2] At clinically effective concentrations, a broad variety of general anaesthetics increase apparent GABA sensitivity and prolong inhibitory post-synaptic current mediated by $GABA_A$ receptors. Advancement in molecular techniques has allowed greater understanding of the action of anaesthetic agents through the use of the 'knock-in' mice model.[3] Conception of the mechanisms of action of many drugs routinely given in the operating room can be improved by the use of protein biomarker technology (such as protein microarray chips).[4] A greater understanding of the mechanisms of anaesthesia will allow the development of more selective anaesthetics to achieve maximal clinical efficacy with minimal adverse effects.

REGIONAL ANAESTHESIA

Regional anaesthesia provides a substitute for general anaesthesia. Alternatively, it can be used to supplement general anaesthesia and provide postoperative analgesia. There is continuous development and refinement of regional anaesthetic techniques for various types of surgery, as well as for continuous regional analgesia.[5] The quality of blockade and analgesia depends on accurate administration of local anaesthetic around the intended nerve structures. The use of nerve stimulation and insulated needles plus the development of ultrasound guidance (with an accurate depiction of the underlying anatomy) allows for precise needle placement.[6] Ultrasound helps monitor the real-time

administration of local anaesthetics or analgesics.[6] Ultrasound or even computed tomography-guided nerve block techniques are particularly useful when the underlying anatomy is complex.[7–10]

Regional anaesthesia precludes the disadvantages seen with general anaesthesia (intubation, long recovery, postoperative nausea and vomiting (PONV), impaired oxygenation and depressed ventilation), It has been successfully used in the fields of obstetrics and in lower-extremity, cardiothoracic,[11–13] breast [14] and laparoscopic surgeries.[15] The risks of anaesthetic and surgical complications are not any higher with regional anaesthesia than with general anaesthesia.[14] However, it is not without its risks, including drug adverse effects, such as cardiovascular toxicity and neurotoxicity.

NEURAXIAL ANAESTHESIA/ANALGESIA

Combining the use of spinal and epidural techniques (CSE) has been gaining popularity over recent years.[16] It provides rapid onset of anaesthesia without increasing the complications.[17] Recent evidence shows that lower doses provide adequate analgesia while reducing the incidence of motor block.[18,19] The spinal needle can be used as a guide for the advancement of epidural needle and prevent the epidural catheter from puncturing the dura.[20] A lower incidence of unintentional 'wet tap' has been shown with this technique. Fetal/neonatal bradycardia is occasionally seen with CSE technique, but is not associated with increased rates of emergency caesarean sections.[21]

In elderly and frail patients, in whom general or epidural anaesthesia may be too risky,[22] continuous spinal anaesthesia (CSA) has recently regained popularity.[23] CSA offers haemodynamic stability, as hypotension is less likely with CSA when compared with CSE.[24,25] However, with any neuraxial administration, hypotension and haematoma formation remain concerns that deserve further attention and research.[24] In neuraxial opioid analgesia, opioid physicochemical properties determine efficacy and safety. Intrathecal morphine, fentanyl and sufentanil are most commonly used.[26] Other analgesic adjuvants include clonidine, dexmedetomidine and adrenaline, all working through α-adrenergic receptors.[26] Other agents in the early stages of investigation for neuraxial analgesia include neostigmine, ketamine, midazolam, adenosine and ziconotide.[26]

NEW DRUGS

The quest for safety has long been a central part of the search for new anaesthetic/analgesic agents. Recent fields examined include the inert gases, the racaemic mixtures (ketamine, ropivacaine, levobupivacaine), the coxibs and the cyclodextrins (Table 1).

Xenon

Of all the inert gases, only xenon has considerable anaesthetic properties under normobaric conditions.[27] Xenon's anaesthetic effect is possibly achieved through the non-competitive antagonism of *N*-methyl-D-aspartate receptor.[25] It is highly lipid soluble with a very low blood/gas partition coefficient (0.14)[28] that makes induction of and emergence from anaesthesia more rapid compared with other inhalational anaesthetic agents.[27] Xenon has also been shown to possess cardioprotective and neuroprotective effects.[29,30] It may prove beneficial in patients at high risk for neurological or cardiac damage during surgery. With the advancement in anaesthetic delivery systems, the cost–benefit of using xenon gas may in future justify its use in high-risk surgical patients.

Table 1. New drugs in clinical and research development in anaesthesia and in analgesia

Clinical anaesthesia	New drugs
Racaemic mixtures	Ketamine Ropivacaine, Levobupivacaine
Adenosine-1 receptor agonists	Adenosine
Local anaesthetic toxicity	Intralipid
Research development in anaesthesia	
Inert gases	Xenon
Cyclodextrins	Sugammadex
Clinical analgesia	
Cyclo-oxgenase 2 inhibitors	Paracoxib Etoricoxib Lumaricoxib
Paracetamol	I.v. paracetamol
Vanilloid receptor 1 (TRPV1) activator	Capsaicin
Encapsulation matrices	Liposomes (bupivacaine, morphine)
Second-generation anticonvulsants	Pregabalin
N-type calcium channel antagonist	Intrathecal ziconotide
Research development in analgesia	
Nitric oxide-releasing paracetamol	Nitroxyparacetamol
Encapsulation matrices	Microspheres
Endocannabinoids	CB2 cannabinoid receptor agonists CB1 cannabinoid receptor agonists
Sodium channel blockers	Neuronal voltage-gated sodium channel blockers (Nav 1.3, Nav 1.7, Nav 1.8 and Nav 1.9 blockers)
Selective potassium channel openers	

Ketamine

The availability of the stereoisomer of ketamine with its increased potency and lower incidence of psychomimetic adverse effects in equianalgesic doses (compared with the racemate) has increased its non-anaesthetic use as an adjunct analgesic.[31]

Cyclo-oxgenase 2 inhibitors

Provided there are no contraindications, the use of the cyclo-oxgenase 2 (COX-2) inhibitors (the coxibs) preoperatively show clear benefits in terms of reduced postoperative pain, analgesic consumption and patient satisfaction.[32] With their chronic use, peptic ulceration remains a reduced but significant adverse effect.[33] Their lack of antiplatelet effects is important in patients on anticoagulants and in neuraxial blockade.[33] COX-2 inhibitors may not produce bronchospasm (at analgesic doses), but may have similar adverse effects as general non-steroidal anti-inflammatory drugs on renal function.[33] More trials are needed to determine their possible prothrombotic effect.

Local anaesthetics

With regard to local anaesthetics, the main focus has been on the development of the enantiomer-specific compounds, ropivacaine

and levobupivacaine. These provide similar efficacy to bupivacaine in peripheral and central nerve blockade, but with reduced risk of severe cardiotoxicity.[34] Human studies have borne this out with levobupivacaine having fewer effects than bupivacaine on QRS prolongation, central nervous system symptoms and electrocardiograph excitation.[34]

There has been no effective antidote for toxic doses of local anaesthetics. Recently, intralipid was shown to effectively reverse local anaesthetic toxicity in the animal model by hastening the loss of bupivacaine from cardiac tissue.[35,36] Several human case reports using a bolus of 20% intralipid followed by an intralipid infusion show promising efficacy.[37,38] As other effective alternatives have not been found, the use of intralipid is worth considering in the management of local anaesthetic toxicity.[39]

Adenosine

Adenosine-1 receptors play a role in antinociception in the spinal cord.[40] The direct administration of adenosine reduces the amount of intraoperative volatile anaesthetic required and contributes to postoperative pain relief.[41] An additional advantage of adenosine is its cardioprotective effect, making it an attractive future option as part of a balanced anaesthetic technique.[42]

Sugammadex

Over the past decades, the search for short termination of action of non-depolarizing muscle relaxants has continued. Sugammadex (Org 25969) is a cyclodextrin.[43] It forms a tight complex with aminosteroid-based non-depolarizing muscle relaxants (rocuronium, pancuronium, vecuronium). Animal and human studies show a rapid dose-dependent decrease in the concentration of free and bound non-depolarizing muscle relaxants.[44,45] It is devoid of the cardiovascular side-effects associated with acetylcholinesterase inhibitors such as neostigmine. Continued research is required to clarify the role of sugammadex before this termination technique can replace the standard use of succinylcholine for short-term muscle relaxation.[46]

PRECONDITIONING

Anaesthetic agents interact with the underlying pathological mechanisms of ischaemia reperfusion injury and protect the myocardium by a preconditioning mechanism.[47] Volatile anaesthetics activate ATP-sensitive potassium channels (similar to ischaemia-induced preconditioning) thereby providing a cardioprotective effect.[48–50] Preconditioning by volatile anaesthetics involves the activation of protein kinase C and mitogen-activated protein kinases. Transcription factors are activated, resulting in the induction of specific genes in the heart.[51] The effects are most evident when the volatile agent is given throughout the entire procedure.[52] The anaesthetist may therefore substantially influence the critical situation of ischaemia-reperfusion during surgery by choosing the appropriate anaesthetic agent.

IMMUNE RESPONSE

Knowledge of the host immune response to anaesthesia/analgesia and surgery needs to be integrated with the role of immunity in general in the progression of many of the chronic diseases.[53] Volatile anaesthetics appear to suppress effector functions of both the innate and adaptive immunity and may facilitate the proliferation of tumour and certain neurodegenerative disease proteins.[54] Local anaesthetics in turn have been shown to have potent anti-inflammatory properties.[54] Some of the new synthetic opioids are devoid of immunosuppressive functions seen with morphine.[55] There remains a need to examine how genetic diversity or acquired defects alter the immune response to tissue injury and infection.[53] This will improve risk stratification and create possible pre-emptive therapies.

TARGET-CONTROLLED INFUSIONS

Progress in computing technology has allowed the development of target-controlled infusion (TCI) devices, with drugs delivered to achieve specific predicted target blood drug concentrations.[56] A set of pharmacokinetic parameters is selected using computer simulation of a known infusion scheme. The selected model is incorporated into a computer-compatible infusion pump. Clinical trials with such systems provide appropriate target concentrations.[56] TCI allows for the administration of small doses of short-acting anaesthetic drugs, such as opioids (remifentanil and fentanyl) and propofol.[57] The use of TCI has been extended to include paediatric anaesthesia and sedation.

MONITORING

Continuous electronic physiological monitoring is core to the safe delivery of anaesthesia during surgery. Devices are being developed that can assess depth of sedation and anaesthesia, stroke volume, cardiac output, systemic vascular resistance, cerebral haemodynamic and metabolic variables.[58] Some new ventilators are capable of monitoring lung mechanics and of automatically adjusting the ventilator settings to prevent ventilator associated lung injury or to aid weaning.[58] New monitors include cerebral microdialysis to provide online analysis of tissue biochemistry.[58] Novel imaging methods include positron emission tomography and functional magnetic resonance imaging.[58]

Non-invasive

Non-invasive monitoring is increasingly being developed for use in anaesthesia. For example, the use of continuous cerebral oximetry protects against the risk of intraoperative cerebral ischaemia.[59] Aortic blood flow can be determined with the use of non-invasive oesophageal echo-Doppler monitoring.[60] Thoracic bioimpedance has been used as well to investigate haemodynamic changes.[61]

Depth of anaesthesia

Over the past 10 years, depth of anaesthesia monitoring has emerged to aid anaesthetists by the development of processed electroencephalographic methods, such as bispectral index, mid-latency auditory-evoked potentials (AEP), and spectral entropy.[62–64] These correlate well to clinical observed level of consciousness.[62–64] These monitoring techniques improve the titration of both inhaled and i.v. anaesthetic agents by avoiding excessive anaesthesia and awareness, promoting faster emergence from anaesthesia, and managing conscious and deep sedation.[65]

Auditory evoked potentials form an electrical manifestation of the brain response to an auditory stimulus. Mid-latency auditory evoked potentials as well as the coherent frequency of the auditory evoked potential are useful for monitoring depth of anaesthesia.[66] It is possible to acquire and process raw electroencephalograph

(EEG) and frontal electromyogram signals and produce two spectral entropy-based indices (namely response entropy and state entropy).[67] The M-Entropy module provides useful information on the cortical state of the patient during general anaesthesia. It acts as an indirect measure of the adequacy of analgesia.[68] With the use of these new monitoring technologies, closed loop anaesthesia in the true sense has finally emerged.

CLOSED LOOP SYSTEMS

In closed or rebreathing circuits, fresh gas supply matches uptake. A lower fresh gas flow rate is therefore used. Humidity and temperature are conserved. In recent years, new computer-assisted control of gas delivery has dramatically improved the gas composition in closed circuits. Fast gas analysers and appropriate algorithms regulate the exact amount of volatile and fresh gas injected into the system. This minimizes the difference between the actual volatile gas concentration and vaporizer setting seen in the traditional closed loop low-flow system. Closed loop systems are able to reach and maintain a preset target.[69] The computer program takes over the role of dose administration while the anaesthetist only enters the desirable level to be maintained. Closed-loop feedback allows the realization of 'quantitative closed-system anaesthesia' in the operating room.[70,71]

To monitor muscle relaxation, a closed-loop muscle relaxation system can be formed by the connection of a muscle relaxation monitor (TOF Watch SX; Organon Schering-Plough, Kenilworth, NJ, USA) to a laptop computer.[72] A controller algorithm programme then communicates with a syringe pump.[72]

The linking of EEG monitoring to TCI for closed loop anaesthesia remains a research tool. Nunes *et al.* recently developed a fuzzy relational classifier that uses AEP features to classify the depth of anaesthesia.[73] It is a machine-learning model based on fuzzy clustering and fuzzy relationship that somehow mimics human thinking.

AIRWAY MANAGEMENT

In addition to fibre-optic airway devices, supraglottic airway devices have revolutionized airway management in anaesthesia over the last 15 years. Examples include the classic, intubating and Proseal (LMA North America, Inc., San Diego, CA, USA) laryngeal mask airway, the Combitube (Tyco-Kendall, Mansfield, MA, USA), the laryngeal tube, and laryngeal tube sonda mark I and II.[74] The Glidescope (Verathon Inc., Bothell, WA, USA) is a new videolaryngoscope.[75] It has a digital camera incorporated in its blade that displays a view of the vocal cords on a monitor. This allows visual placement of a tracheal tube. Improved designs include the paediatric ProSeal–Laryngeal mask airway[76] and the Microcuff (Kimberly-Clark Health Care, Roswell, GA, USA) paediatric endotracheal tube.[76]

TRANSOESOPHAGEAL ECHOCARDIOGRAPHY

Transoesophageal echocardiography (TOE) has proved useful to anaesthetists in guiding therapy in haemodynamically unstable patients in the operating room and intensive care unit. TOE provides real-time dynamic information about the anatomy and physiology of the whole heart.[77] It is of value in the management of patients undergoing procedures (including cardiac valvular repair), in surgery for endocarditis and in surgery of the thoracic aorta. It contributes useful information in a wide range of cardiac pathologies.[77]

POSTOPERATIVE NAUSEA AND VOMITING

Postoperative nausea and vomiting remains problematic to every anaesthetist and surgeon. There is strong evidence that volatile anaesthetics (like opioids) are emetogenic with no meaningful differences between halothane, enflurane, isoflurane, sevoflurane and desflurane.[78] Various anti-emetic strategies are associated with a reduction rate of approximately 25–30%.[79] However, when a propofol technique is substituted for a volatile anaesthetic technique, the risk for PONV is reduced by approximately one-fifth.[78] Interestingly, all anti-emetics (dexamethasone, droperidol and ondansetron) work independently, so a combination benefit can be derived.[80] If PONV is a serious problem, general anaesthesia can be avoided by using a regional, opioid-free anaesthetic instead.[79]

PATIENT SAFETY AND RISK PREVENTION

Anaesthesia was one of the first medical professions to treat patient safety as an independent problem. Preoperative evaluation carried out by anaesthetists aims primarily to estimate the risk of perioperative complications and to create opportunities to optimize the patient's condition before surgery.[81] Patient safety is primarily determined by quality of systems of care. There has been steady progress in anaesthesia safety because of the development of performance standards, an increase in error reporting, integration of information technology and improved safety systems.[82] This has led to a 10-fold reduction in anaesthesia-related deaths over the past few decades, despite the increase in more challenging operations and the number of older and sicker patients. According to the Institute of Medicine's 1999 report entitled *To err is human*, '… anesthesiology has successfully reduced anesthesia mortality rates from two deaths per 10 000 anesthetics administered, to one death per 200 000 to 300 000 anesthetics administered'.[83]

ADVANCES IN ANAESTHETIC-LED ACUTE PAIN SERVICES

The occurrence of postoperative pain remains problematic. In 2003, Apfelbaum found that 80% of patients still experience postoperative pain.[84] Acute pain management services first entered clinical practice in the late 1980s.[85] Anaesthetists have played an important role in this interdisciplinary approach to managing postoperative pain.[86] Evidence of earlier discharge with the use of an acute pain service has been shown.[87,88]

Inadequately relieved postoperative pain leads to complications, such as deep vein thrombosis, lung infections and myocardial ischaemia, which may extend hospital stay.[89] New analgesics and analgesic drug delivery systems are being developed. For example, the use of i.v. paracetamol avoids absorption and bioavailability variability and produces more predictable plasma paracetamol concentrations than the oral route.[90] Nitroxyparacetamol (or nitroacetaminophen) is a new, potent nitric oxide-releasing version of paracetamol that has analgesic and anti-inflammatory properties.[33,91] It should prove a useful analgesic for patients with paracetamol-induced liver damage. The anticonvulsant gabapentin has shown analgesic efficacy in several surgical procedures, particularly to reduce post-surgical neuropathic pain.[92] Early studies with its successor, pregabalin are in progress.

Advances in neurobiology and clinical medicine have established that the fetus and newborn may experience acute and even

chronic pain.[93] Many scales have been developed in an attempt to standardize pain measurement in neonates.[93] Recently, attention has been paid to the short-term and long-term outcomes of premature infants and newborns exposed to noxious stimuli. These include simple heel prick, invasive intubation and surgery. Repeated or prolonged painful experiences are linked to deleterious outcomes in preterm neonates.[93] It could alter the development of the nervous system and lead to abnormal pain behaviour in later life.[94,95] This shows the importance of good analgesia during any procedure in neonates.[94,95]

CHRONIC PAIN SERVICES

Anaesthetists often lead the medical specialist team involved in chronic pain management. In some patients, the hyperphenomena (primary and secondary hyperalgesia, mechanical allodynia) that are normal in the first days or weeks after surgery, do not regress, but persist beyond the usual course of an acute surgical injury.[96] Acute persistent pain soon becomes chronic pain.[96] Chronic pain demands a greater use of the health resources and has proved to be a major public health burden.[97] Unrelieved postoperative pain and severe perioperative pain have been shown to be risk factors for the development of chronic pain.[98] This emphasizes the need for effective perioperative pain management.

There has been tremendous progress in pain medicine (particularly interventional pain medicine) enhancing the contribution of the anaesthetist in managing post-surgical pain syndromes. Advances in neuroimaging techniques (positron emission tomography, functional magnetic resonance imaging) help identify brain mechanisms for more effective treatments for chronic pain. Rapid progress is being made towards the development of gene therapy.[80] For example, viral vector-mediated gene transfer achieves focal production of short-lived analgesic peptides (or growth factors). This prevents disc degeneration and promotes chondrocyte and disc regeneration.[99] This should soon have clinical application for both the anaesthetist and the surgeon involved in pain medicine.[99]

New techniques in neuromodulation have promoted existing teamwork between the anaesthetist and the surgeon. The reduced demand for health-care resources by patients receiving neuromodulation (peripheral nerve stimulation, spinal cord stimulation) suggests substantial long-term economic benefits in patients with neuropathic pain and chronic refractory angina receiving these.[100] Anaesthetists may aid the orthopaedic surgeons by the radiofrequency heating of annular tears, leading to an improvement in the pain of internal disc disruption.[101] In addition they can help out by carrying out kyphoplasty, a minimally invasive technique that appears to improve both pain and function in patients with vertebral fractures because of osteoporosis.[102]

New analgesic delivery systems are being developed for anaesthetists to assist surgeons in perioperative pain relief. Progress is being made in the ability to combine local anaesthetics with liposomes (bupivacaine, morphine) and polymer microspheres.[103] Systems designed to transiently circumvent the barrier function of the stratum corneum, using iontophoresis and sonophoresis, will expand the range of drugs that can be delivered transdermally.[91] New analgesic drugs are being studied as well to treat post-surgical neuropathic pain. These include pregabalin, a novel alpha (2)-delta ligand[104]; ziconotide, a drug derived from a snail toxin that works on the calcium channels[105] and endocannabinoids, that naturally suppress nociceptive neurotransmission.[106]

FUTURE FOCUS

How could anaesthetists aid the patient undergoing surgery in future? Software could be developed to integrate patient monitoring and response to anaesthesia and surgery, resulting in an early warning system that alerts the anaesthetist to impending disaster.[107] New techniques like nanotechnology could enable precise timing and site of drug delivery.[107] Delivery systems under development could deposit drugs at the desired site of action, control their rate of release, and to neutralize overdose, bind and eliminate previously given drugs.[107] Emerging applications could be developed by pharmacogenomic research as well. In post-surgical pain medicine, Anaesthetists could make use of new molecular targets, such as sodium channel blockers (Nav 1.3, Nav 1.7 and Nav 1.8) [108]; potassium channel openers in sensory neurons[109]; N-type calcium channels (Cav 2.2) blockers[109]; P2X4 and P2X7 receptor antagonists in microglia[110]; vanilloid receptor-1 antagonists[111,112]; and the cannabinoid-2 receptor agonists.[111,113]

CONCLUSION

Anaesthesia historically grew out of surgery and the two disciplines continue to work in close partnership. Anaesthetists and surgeons form an integrated team linking together to do their utmost for the good of the patient. This relationship plays an important role in enabling patient safety and avoiding errors. Of importance to the surgeon are the recent developments in anaesthetic technology and the advances in drugs and monitoring methods. As illustrated in this manuscript, these developments have accelerated and altered the work carried out in the operating room. In addition, evidence is just beginning to emerge on the relation between specific anaesthetics and anaesthetic techniques and long-term clinical outcomes after surgery.[114]

REFERENCES

1. Urban BW. Current assessment of targets and theories of anaesthesia. *Br. J. Anaesth*. 2002; **89**: 167–83.
2. Clark M. Sensitivity of the rat hippocampal GABA (A) receptor alpha 4 subunit to electroshock seizures. *Neurosci. Lett*. 1998; **250**: 17–20.
3. Jurd R, Arras M, Lambert S *et al*. General anesthetic actions in vivo strongly attenuated by a point mutation in the GABA(A) receptor beta3 subunit. *FASEB J*. 2003; **17**: 250–52.
4. Atkins JH, Johansson JS. Technologies to shape the future: proteomics applications in anesthesiology and critical care medicine. *Anesth. Analg*. 2006; **102**: 1207–16.
5. Rosenberg PH. Future of regional anaesthesia. *Acta Anaesthesiol. Scand*. 2005; **49**: 913–18.
6. Marhofer P, Greher M, Kapral S. Ultrasound guidance in regional anaesthesia. *Br. J. Anaesth*. 2005; **94**: 7–17.
7. De Cicco M, Matovic M, Bortolussi R *et al*. Celiac plexus block: injectate spread and pain relief in patients with regional anatomic distortions. *Anesthesiology* 2001; **94**: 561–5.
8. Eisenberg E, Carr DB, Chalmers TC. Neurolytic celiac plexus block for treatment of cancer pain: a meta-analysis. *Anesth. Analg*. 1995; **80**: 290–95.
9. Schneider-Kolsky ME, Pike J, Connell DA. CT-guided suprascapular nerve blocks: a pilot study. *Skeletal Radiol*. 2004; **33**: 277–82.
10. Shanahan EM, Smith MD, Wetherall M *et al*. Suprascapular nerve block in chronic shoulder pain: are the radiologists better? *Ann. Rheum. Dis*. 2004; **63**: 1035–40.
11. Hemmerling TM, Noiseux N, Basile F, Noel MF, Prieto I. Awake cardiac surgery using a novel anesthetic technique. *Can. J. Anaesth*. 2005; **52**: 1088–92.

12. Kessler P, Neidhart G, Bremerich DH *et al*. High thoracic epidural anesthesia for coronary artery bypass grafting using two different surgical approaches in conscious patients. *Anesth. Analg*. 2002; **95**: 791–7.
13. Kirali K, Kocak T, Guzelmeric F, Goksedef D, Kayalar N, Yakut C. Off-pump awake coronary revascularization using bilateral internal thoracic arteries. *Ann. Thorac. Surg*. 2004; **78**: 1598–602.
14. Singh AP, Tewari M, Singh DK, Shukla HS. Cervical epidural anesthesia: a safe alternative to general anesthesia for patients undergoing cancer breast surgery. *World J. Surg*. 2006; **30**: 2043–7.
15. Kruschinski D, Homburg S. Lift-(gasless) laparoscopic surgery under regional anesthesia. *Surg. Technol. Int*. 2005; **14**: 193–6.
16. Burnstein R, Buckland R, Pickett JA. A survey of epidural analgesia for labour in the United Kingdom. *Anaesthesia* 1999; **54**: 634–40.
17. Hughes D, Simmons SW, Brown J, Cyna AM. Combined spinal-epidural versus epidural analgesia in labour. *Cochrane Database Syst. Rev*. 2003; **4**: CD 003401.
18. Lee BB, Ngan Kee WD, Hung VY, Wong EL. Combined spinal-epidural analgesia in labour: comparison of two doses of intrathecal bupivacaine with fentanyl. *Br. J. Anaesth*. 1999; **83**: 868–71.
19. Parpaglioni R, Frigo MG, Sebastiani M *et al*. High volume of subarachnoid levobupivacaine decreases drug requirement in first stage labor analgesia. *Minerva Anestesiol*. 2004; **70**: 809–21.
20. Norris MC, Grieco WM, Borkowski M *et al*. Complications of labor analgesia: epidural versus combined spinal epidural techniques. *Anesth. Analg*. 1994; **79**: 529–37.
21. Albright GA, Forster RM. Does combined spinal-epidural analgesia with subarachnoid sufentanil increase the incidence of emergency cesarean delivery? *Reg. Anesth*. 1997; **22**: 400–405.
22. Michaloudis D, Petrou A, Bakos P *et al*. Continuous spinal anesthesia/analgesia for the perioperative management of high-risk patients. *Eur. J. Anaesthesiol*. 2000; **18**: 239–47.
23. Denny NM, Harrop-Griffiths W. Location, location, location! Ultrasound imaging in regional anaesthesia. *Br. J. Anaesth*. 2005; **94**: 1–3.
24. Klimscha W, Weinstabl C, Ilias W *et al*. Continuous spinal anesthesia with a microcatheter and low-dose bupivacaine decreases the hemodynamic effects of centroneuraxis blocks in elderly patients. *Anesth. Analg*. 1993; **77**: 275–80.
25. Labaille T, Benhamou D, Westermann J. Hemodynamic effects of continuous spinal anesthesia: a comparative study between low and high doses of bupivacaine. *Reg. Anesth*. 1992; **17**: 193–6.
26. Schug SA, Saunders D, Kurowski I, Paech MJ. Neuraxial drug administration. *CNS Drugs* 2006; **20**: 917–33.
27. Rasmussen LS, Schmehl W, Jakobsson J. Comparison of xenon with propofol for supplementary general anaesthesia for knee replacement: a randomized study. *Br. J. Anaesth*. 2006; **97**: 154–9.
28. Steward A, Allott PR, Cowles AL, Mapleson WW. Solubility coefficients for inhaled anaesthetics for water, oil and biological media. *Br. J. Anaesth*. 1973; **45**: 282–93.
29. Weber NC, Toma O, Wolter JI *et al*. The noble gas xenon induces pharmacological preconditioning in the rat heart in vivo via induction of PKC-epsilon and p38 MAPK. *Br. J. Pharmacol*. 2005; **144**: 123–32.
30. Rajakumaraswamy N, Ma D, Hossain M. Neuroprotective interaction produced by xenon and dexmedetomidine on in vitro and in vivo neuronal injury models. *Neurosci. Lett*. 2006; **409**: 128–33.
31. Geisslinger G, Hering W, Thomann P, Knoll R, Kamp HD, Brune K. Pharmacokinetics and pharmacodynamics of ketamine enantiomers in surgical patients using a stereoselective analytical method. *Br. J. Anaesth*. 1993; **70**: 666–71.
32. Straube S, Derry S, McQuay HJ, Moore RA. Effect of preoperative Cox-II-selective NSAIDs (coxibs) on postoperative outcomes: a systematic review of randomized studies. *Acta Anaesthesiol. Scand*. 2005; **49**: 601–13.
33. Power I. Recent advances in postoperative pain therapy. *Br. J. Anaesth*. 2005; **95**: 43–51.
34. Van de Velde M, Dreelinck R, Dubois J. Determination of the full dose-response relation of intrathecal bupivacaine, levobupivacaine, and ropivacaine, combined with sufentanil, for labor analgesia. *Anesthesiology* 2007; **106**: 149–56.
35. Weinberg G, Ripper R, Feinstein DL, Hoffman W. Lipid emulsion infusion rescues dogs from bupivacaine-induced cardiac toxicity. *Reg. Anesth. Pain Med*. 2003; **28**: 198–202.
36. Weinberg GL, VadeBoncouer T, Ramaraju GA, Garcia-Amaro MF, Cwik MJ. Pretreatment or resuscitation with a lipid infusion shifts the dose-response to bupivacaine-induced asystole in rats. *Anesthesiology* 1998; **88**: 1071–5.
37. Litz RJ, Popp M, Stehr SN, Koch T. Successful resuscitation of a patient with ropivacaine-induced asystole after axillary plexus block using lipid infusion. *Anaesthesia* 2006; **61**: 800–801.
38. Rosenblatt MA, Abel M, Fischer GW, Itzkovich CJ, Eisenkraft JB. Successful use of a 20% lipid emulsion to resuscitate a patient after a presumed bupivacaine-related cardiac arrest. *Anesthesiology* 2006; **105**: 217–18.
39. Picard J, Meek T. Lipid emulsion to treat overdose of local anaesthetic: the gift of the glob. *Anaesthesia* 2006; **61**: 107–9.
40. Sawynok J. Adenosine receptor activation and nociception. *Eur. J. Pharmacol*. 1998; **347**: 1–11.
41. Hayashida M, Fukunaga A, Fukuda K. The characteristics of intravenous adenosine-induced antinociception in a rabbit model of acute nociceptive pain: a comparative study with remifentanil. *Anesth. Analg*. 2006; **103**: 1004–10.
42. Willems L, Ashton KJ, Headrick JP. Adenosine-mediated cardioprotection in the aging myocardium. *Cardiovasc. Res*. 2005; **66**: 245–55.
43. Adam JM, Bennett DJ, Bom A *et al*. Cyclodextrin-derived host molecules as reversal agents for the neuromuscular blocker rocuronium bromide: synthesis and structure-activity relationships. *J. Med. Chem*. 2002; **45**: 1806–16.
44. De Boer HD, van Egmond J, van de Pol F, Bom A, Booij LH. Reversal of profound rocuronium neuromuscular blockade by sugammadex in anesthetized rhesus monkeys. *Anesthesiology* 2006; **104**: 718–23.
45. Sorgenfrei IF, Norrild K, Larsen PB *et al*. Reversal of rocuronium-induced neuromuscular block by the selective relaxant binding agent sugammadex: a dose-finding and safety study. *Anesthesiology* 2006; **104**: 667–74.
46. Kopman AF. Sugammadex: a revolutionary approach to neuromuscular antagonism. *Anesthesiology* 2006; **104**: 631–3.
47. Weber NC, Preckel B, Schlack W. The effect of anaesthetics on the myocardium–new insights into myocardial protection. *Eur. J. Anaesthesiol*. 2005; **22**: 647–57.
48. Conzen PF, Fischer S, Detter C, Peter K. Sevoflurane provides greater protection of the myocardium than propofol in patients undergoing off-pump coronary artery bypass surgery. *Anesthesiology* 2003; **99**: 826–33.
49. De Hert SG, ten Broecke PW, Mertens E *et al*. Sevoflurane but not propofol preserves myocardial function in coronary surgery patients. *Anesthesiology* 2002; **97**: 42–9.
50. Zaugg M, Lucchinetti E, Spahn DR, Pasch T, Schaub MC. Volatile anesthetics mimic cardiac preconditioning by priming the activation of mitochondrial K (ATP) channels via multiple signaling pathways. *Anesthesiology* 2002; **97**: 4–14.
51. Kalenka A, Maurer MH, Feldmann RE, Kuschinsky W, Waschke KF. Volatile anesthetics evoke prolonged changes in the proteome of the left ventricle myocardium: defining a molecular basis of cardioprotection? *Acta Anaesthesiol. Scand*. 2006; **50**: 414–27.

52. Cromheecke S, Pepermans V, Hendrickx E *et al*. Cardioprotective properties of sevoflurane in patients undergoing aortic valve replacement with cardiopulmonary bypass. *Anesth. Analg*. 2006; **103**: 289–96.
53. Meiler SE. Long-term outcome after anesthesia and surgery: remarks on the biology of a newly emerging principle in perioperative care. *Anesthesiol. Clin*. 2006; **24**: 255–78.
54. Homburger JA, Meiler SE. Anesthesia drugs, immunity, and long-term outcome. *Curr. Opin. Anaesthesiol*. 2006; **19**: 423–8.
55. Budd K. Pain management: is opioid immunosuppression a clinical problem? *Biomed. Pharmacother.* 2006; **60**: 310–17.
56. Fanti L, Agostoni M, Arcidiacono PG *et al*. Target-controlled infusion during monitored anesthesia care in patients undergoing EUS: Propofol alone versus midazolam plus propofol. A prospective double-blind randomised controlled trial. *Dig. Liver Dis*. 2007; **39**: 81–6.
57. Wang LP, McLoughlin P, Paech MJ *et al*. Low and moderate remifentanil infusion rates do not alter target-controlled infusion propofol concentrations necessary to maintain anesthesia as assessed by bispectral index monitoring. *Anesth. Analg*. 2007; **104**: 325–31.
58. Thompson JP, Mahajan RP. Monitoring the monitors–beyond risk management. *Br. J. Anaesth*. 2006; **97**: 1–3.
59. Casati A, Fanelli G, Pietropaoli P *et al*. Continuous monitoring of cerebral oxygen saturation in elderly patients undergoing major abdominal surgery minimizes brain exposure to potential hypoxia. *Anesth. Analg*. 2005; **101**: 740–47.
60. Cafiero T, Di Iorio C, Di Minno RM. Non-invasive cardiac monitoring by aortic blood flow determination in patients undergoing hyperthermic intraperitoneal intraoperative chemotherapy. *Minerva Anestesiol*. 2006; **72**: 207–15.
61. Suttner S, Schollhorn T, Boldt J *et al*. Noninvasive assessment of cardiac output using thoracic electrical bioimpedance in hemodynamically stable and unstable patients after cardiac surgery: a comparison with pulmonary artery thermodilution. *Intensive Care Med*. 2006; **32**: 2053–8.
62. van Twest RM. Bispectral index guided timing of intubation without neuromuscular blockade during sevoflurane induction of anaesthesia in adults. *Anaesth. Intensive Care* 2006; **34**: 606–12.
63. Vereecke HE, Vanluchene AL, Mortier EP *et al*. The effects of ketamine and rocuronium on the A-Line auditory evoked potential index, Bispectral Index, and spectral entropy monitor during steady state propofol and remifentanil anesthesia. *Anesthesiology* 2006; **105**: 1122–34.
64. Vakkuri A, Yli-Hankala A, Sandin R *et al*. Spectral entropy monitoring is associated with reduced propofol use and faster emergence in propofol-nitrous oxide-alfentanil anesthesia. *Anesthesiology* 2005; **103**: 274–9.
65. White PF. Use of cerebral monitoring during anaesthesia: effect on recovery profile. *Best Pract. Res. Clin. Anaesthesiol*. 2006; **20**: 181–9.
66. Hadzidiakos D, Petersen S, Baars J *et al*. Comparison of a new composite index based on midlatency auditory evoked potentials and electroencephalographic parameters with bispectral index (BIS) during moderate propofol sedation. *Eur. J. Anaesthesiol*. 2006; **23**: 931–6.
67. Takamatsu I, Ozaki M, Kazama T. Entropy indices vs the bispectral index for estimating nociception during sevoflurane anaesthesia. *Br. J. Anaesth*. 2006; **96**: 620–26.
68. Ellerkmann RK, Soehle M, Alves TM *et al*. Spectral entropy and bispectral index as measures of the electroencephalographic effects of propofol. *Anesth. Analg*. 2006; **102**: 1456–62.
69. Struys MM, De Smet T, Greenwald S *et al*. Performance evaluation of two published closed-loop control systems using bispectral index monitoring: a simulation study. *Anesthesiology* 2004; **100**: 640–47.
70. Baum JA. New and alternative delivery concepts and techniques. *Best Pract. Res. Clin. Anaesthesiol*. 2005; **19**: 415–28.
71. Struys MM, Kalmar AF, De Baerdemaeker LE *et al*. Time course of inhaled anaesthetic drug delivery using a new multifunctional closed-circuit anaesthesia ventilator. In vitro comparison with a classical anaesthesia machine. *Br. J. Anaesth*. 2005; **94**: 306–17.
72. Eleveld DJ, Proost JH, Wierda JM. Evaluation of a closed-loop muscle relaxation control system. *Anesth. Analg*. 2005; **101**: 758–64.
73. Nunes CS, Mahfouf M, Linkens DA, Peacock JE. Modelling and multivariable control in anaesthesia using neural-fuzzy paradigms Part I. Classification of depth of anaesthesia and development of a patient model. *Artif. Intell. Med*. 2005; **35**: 195–206.
74. Cook TM, Hommers C. New airways for resuscitation? *Resuscitation* 2006; **69**: 371–87.
75. Lai HY, Chen IH, Chen A. The use of the Glidescope for tracheal intubation in patients with ankylosing spondylitis. *Br. J. Anaesth*. 2006; **97**: 419–22.
76. Bottcher-Haberzeth S, Dullenkopf A, Gitzelmann CA, Weiss M. Tracheal tube tip displacement during laparoscopy in children. *Anaesthesia* 2007; **62**: 131–4.
77. Kneeshaw JD. Transoesophageal echocardiography (TOE) in the operating room. *Br. J. Anaesth*. 2006; **97**: 77–84.
78. Apfel CC, Kranke P, Katz MH *et al*. Volatile anaesthetics may be the main cause of early but not delayed postoperative vomiting: a randomized controlled trial of factorial design. *Br. J. Anaesth*. 2002; **88**: 659–68.
79. Apfel CC, Stoecklein K, Lipfert P. PONV: a problem of inhalational anaesthesia? *Best Pract. Res. Clin. Anaesthesiol*. 2005; **19**: 485–500.
80. Milligan ED, Langer SJ, Sloane EM *et al*. Controlling pathological pain by adenovirally driven spinal production of the anti-inflammatory cytokine, interleukin-10. *Eur. J. Neurosci*. 2005; **21**: 2136–48.
81. Lemmens LC, van Klei WA, Klazinga NS. The effect of national guidelines on the implementation of outpatient preoperative evaluation clinics in Dutch hospitals. *Eur. J. Anaesthesiol*. 2006; **23**: 962–70.
82. Lanier WL. A three-decade perspective on anesthesia safety. *Am. Surg*. 2006; **72**: 985–9.
83. Scott M. IOM 'To err is human'. Available from URL: http://www.asahq.org/Newletters/2000/03_00/washington0300.html
84. Apfelbaum JL, Chen C, Mehta SS, Gan TJ. Post operative pain experience: results from a national survey suggest postoperative pain continues to be undermanaged. *Anesth. Analg*. 2003; **97**: 534–40.
85. Scavone BM, Sproviero MT, McCarthy RJ *et al*. Development of an objective scoring system for measurement of resident performance on the human patient simulator. *Anesthesiology* 2006; **105**: 260–66.
86. Practice guidelines for acute pain management in the perioperative setting. A report by the American Society of Anesthesiologists Task Force on pain management, acute pain section. *Anesthesiology* 1995; **82**: 1071–81.
87. McDonnell A, Nicholl J, Read SM. Acute pain teams and the management of postoperative pain: a systematic review and meta-analysis. *J. Adv. Nurs*. 2003; **41**: 261–73.
88. Werner MU, Soholm L, Rotboll-Nielsen P, Kehlet H. Does an acute pain service improve postoperative outcome? *Anesth. Analg*. 2002; **95**: 1361–72.
89. Chaney MA. Intrathecal and epidural anesthesia and analgesia for cardiac surgery. *Anesth. Analg*. 2006; **102**: 45–64.
90. Gregoire N, Hovsepian L, Gualano V *et al*. Safety and pharmacokinetics of paracetamol following intravenous administration of 5 g during the first 24 h with a 2-g starting dose. *Clin. Pharmacol. Ther.* 2007; **81**: 401–5.
91. Keeble JE, Moore PK. Pharmacology and potential therapeutic applications of nitric oxide-releasing non-steroidal

anti-inflammatory and related nitric oxide-donating drugs. *Br. J. Pharmacol*. 2002; **137**: 295–310.
92. Dahl JB, Mathiesen O, Moiniche S. 'Protective premedication' an option with gabapentin and related drugs? *Acta Anaesthesiol. Scand*. 2004; **48**: 1130–36.
93. Sharek PJ, Powers R, Koehn A, Anand KJ. Evaluation and development of potentially better practices to improve pain management of neonates. *Pediatrics* 2006; **118**: S78–86.
94. Anand KJ. Clinical importance of pain and stress in preterm neonates. *Biol. Neonate* 1998; **73**: 1–9.
95. Anand KJ, Scalzo FM. Can adverse neonatal experiences alter brain development and subsequent behavior? *Biol. Neonate* 2000; **77**: 69–82.
96. Shipton E, Shipton E. The pain epidemic: some proposed solutions. *N. Z. Med. J*. 2005; **118**: U1627.
97. Eriksen J, Jensen MK, Sjogren P, Ekholm O, Rasmussen NK. Epidemiology of chronic non-malignant pain in Denmark. *Pain* 2003; **106**: 221–8.
98. Shipton EA, Tait B. Flagging the pain: preventing the burden of chronic pain by identifying and treating risk factors in acute pain. *Eur. J. Anaesthesiol*. 2005; **22**: 405–12.
99. Evans C. Potential biologic therapies for the intervertebral disc. *J. Bone Joint Surg. Am*. 2006; **88**: S95–8.
100. Taylor RS. Spinal cord stimulation in complex regional pain syndrome and refractory neuropathic back and leg pain/failed back surgery syndrome: results of a systematic review and meta-analysis. *J. Pain Symptom Manage*. 2006; **31**: S13–19.
101. Zhou Y, Abdi S. Diagnosis and minimally invasive treatment of lumbar discogenic pain–a review of the literature. *Clin. J. Pain* 2006; **22**: 468–81.
102. Pflugmacher R, Beth P, Schroeder RJ *et al*. Balloon kyphoplasty for the treatment of pathological fractures in the thoracic and lumbar spine caused by metastasis: one-year follow-up. *Acta Radiol*. 2007; **48**: 89–95.
103. Holt DV, Viscusi ER, Wordell CJ. Extended-duration agents for perioperative pain management. *Curr. Pain Headache Rep*. 2007; **11**: 33–7.
104. Tarride JE, Gordon A, Vera-Llonch M *et al*. Cost-effectiveness of pregabalin for the management of neuropathic pain associated with diabetic peripheral neuropathy and postherpetic neuralgia: a Canadian perspective. *Clin. Ther.* 2006; **28**: 1922–34.
105. Stanton-Hicks M, Kapural L. An effective treatment of severe complex regional pain syndrome type 1 in a child using high doses of intrathecal ziconotide. *J. Pain Symptom Manage*. 2006; **32**: 509–11.
106. Mitrirattanakul S, Ramakul N, Guerrero AV *et al*. Site-specific increases in peripheral cannabinoid receptors and their endogenous ligands in a model of neuropathic pain. *Pain* 2006; **126**: 102–14.
107. Modell JH. Assessing the past and shaping the future of anesthesiology. *Anesthesiology* 2005; **102**: 1050–57.
108. Wang SY, Mitchell J, Wang GK. Preferential block of inactivation-deficient Na+ currents by capsaicin reveals a non-TRPV1 receptor within the Na+ channel. *Pain* 2007; **127**: 73–83.
109. Cheng JK, Chen CC, Yang JR, Chiou LC. The antiallodynic action target of intrathecal gabapentin: Ca2+ channels, KATP channels or N-methyl-d-aspartic acid receptors? *Anesth. Analg*. 2006; **102**: 182–7.
110. Michel AD, Xing M, Thompson KM, *et al*. Decavanadate, a P2X receptor antagonist, and its use to study ligand interactions with P2X7 receptors. *Eur. J. Pharmacol*. 2006; **534**: 19–29.
111. Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. *Lancet* 2006; **367**: 1618–25.
112. Kanai Y, Nakazato E, Fujiuchi A *et al*. Involvement of an increased spinal TRPV1 sensitization through its up-regulation in mechanical allodynia of CCI rats. *Neuropharmacology* 2005; **49**: 977–84.
113. Sagar DR, Kelly S, Millns PJ *et al*. Inhibitory effects of CB1 and CB2 receptor agonists on responses of DRG neurons and dorsal horn neurons in neuropathic rats. *Eur. J. Neurosci*. 2005; **22**: 371–9.
114. Parker BM. Anesthetics and anesthesia techniques: impacts on perioperative management and postoperative outcomes. *Cleve. Clin. J. Med*. 2006; **73**: S13–17.