

SURGICAL STRESS: THE ROLE OF PAIN AND ANALGESIA

H. KEHLET

The endocrine, metabolic and inflammatory responses to injury and infection are composed of a variety of physiological changes often grouped together and called the surgical stress response. Over the past few decades, detailed knowledge has accumulated on this response and has allowed consideration and development of therapeutic manoeuvres designed to assist or manipulate the patient's response to a surgical operation in order to improve postoperative morbidity.

Since relief of postoperative pain is supposed to be a prerequisite for improved postoperative outcome, this paper summarizes the effects on the surgical stress response of the available techniques. A short review of the clinical implications of postoperative pain relief will also be given. It is not intended to give a complete bibliography of this vast topic, but primarily to bring recent findings into balance with previous data. The reader is therefore referred to recent reviews of the surgical stress response, including release mechanisms and modifying factors [7,13,14,16,17,25].

RELEASE MECHANISMS OF THE SURGICAL STRESS RESPONSE

Although the exact nature and relative importance of the various signals that may initiate, amplify, sustain and complete the stress response remain to be settled, recent studies have shed more light on the relative roles of afferent neural and humoral stimuli.

The nociceptive signal to the central nervous system is transmitted from the site of surgery primarily by small myelinated (A-delta) and unmyelinated (C) sensory afferent fibres [27,45]. Recent studies with regional anaesthesia producing total pain relief (which was assumed to include block of these fibres) suggest that fast

conducting fibres may also be involved in the initial endocrine and metabolic response [14,16]. The relative roles of somatosensory and sympathetic afferents has not been specifically addressed, because the available blocking techniques are inadequate and non-specific. However, somatosensory and sympathetic afferents are probably more important in releasing the response than are vagal afferents [14,16]. The mechanism that sustains the response after injury has not been settled either, but functional changes within the peripheral and central nervous system leading to hypersensitivity in the response to nociceptive stimuli [41] may be of importance.

Although the neural stimulus is a major release mechanism for the surgical stress response, various humoral factors contribute, especially during major procedures and infection. The nature of the substances released at the site of trauma and from macrophages has been studied extensively during recent years, but a clear picture has not yet emerged. Of these, macrophage-derived peptides like interleukins and tumour necrosis factor seem to be most important in releasing various components of the stress response [16,22,25]. Although neural and humoral factors may in themselves be responsible for several aspects of the response, both inflammatory and endocrine (predominantly neurally mediated) factors must be activated to produce the full response.

MODIFYING EFFECT OF POSTOPERATIVE PAIN RELIEF

The various techniques available to provide pain relief in surgical patients and thereby eventually modify the surgical stress response are shown in figure 1.

Antagonists of peripheral mediators of pain

Injury leads to release of several endogenous algic substances (histamine, serotonin, prostaglandins, leukotrienes, substance P, kinins *etc.*) which may facilitate the afferent nociceptive

HENRIK KEHLET, M.D., PH.D., Department of Surgical Gastroenterology, Hvidovre University Hospital, DK-2650 Hvidovre, Denmark.

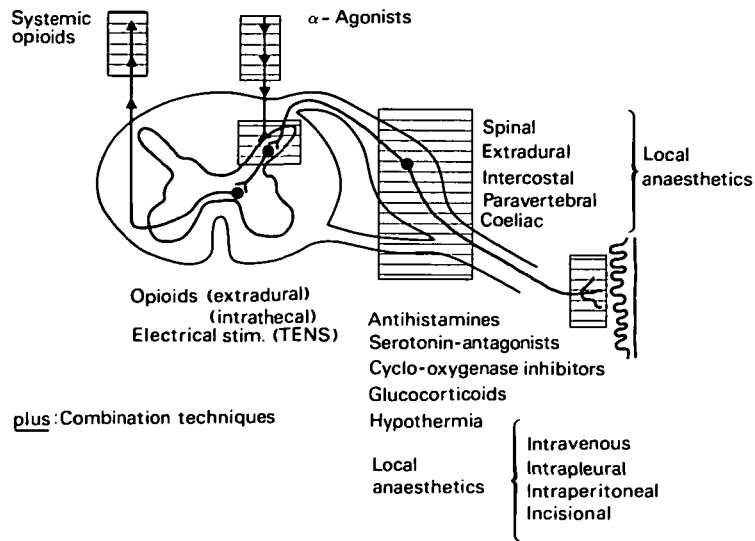


FIG. 1. Postoperative analgesic techniques which may alter the surgical stress response.

neural signal [27,45]. The analgesic effect of treatment with antihistamines or serotonin antagonists has not been settled, but is probably unimportant clinically. Furthermore, the metabolic effect of such an intervention is also negligible with regard to nitrogen turnover [38], temperature, acute phase and leucocytic responses [31].

The analgesic effect of cyclo-oxygenase inhibitors (indomethacin, ibuprofen *etc.*) is moderate [15,32], but the metabolic modification produced by these compounds is interesting because various inflammatory and cardiovascular responses may be attenuated. Thus after endotoxin, ibuprofen decreased pyrexia, tachycardia, increased metabolic rate and stress hormone release, while leucocytosis and acute phase protein changes were unaffected [29]. Other studies suggested that indomethacin could decrease postoperative nitrogen excretion [1], and pyrexia [32,33], while the effects on leucocytosis and acute phase proteins are probably negligible [32,33]. No systematic study has been performed to compare the modifying effect of various non-steroid anti-inflammatory agents on the surgical stress response. Neither is any clinical study available on pain relief produced by substance P antagonist administration or its eventual modification of the stress response.

The analgesia produced by hypothermia is well known in patients with burn injury, but this has

not been utilized in surgical patients. Nevertheless, recent observations during hypothermic anaesthesia in experimental and clinical studies suggest that postoperative proteolysis may be attenuated [12]. Further studies, also addressing a possible modification of the inflammatory reaction, should be performed.

Glucocorticoids are potent inhibitors of all the metabolites of the arachidonic acid cascade as well as of several of the metabolically active macrophage-derived peptides. Although glucocorticoids may have potential side effects on wound healing and immunofunction, it is most interesting that a single, large preoperative dose of methylprednisolone led to improved pain relief and reduced need for extradural analgesics. In addition, the hyperthermic response was blocked and postoperative impairment in pulmonary function and fatigue decreased [Schulze and colleagues, in preparation]. Obviously, further studies are necessary, but it should be emphasized that glucocorticoids remain the only therapeutic agents with potential multi-inhibitory effects on the various components of the stress response.

Local anaesthetics may be applied directly to the nociceptors by a number of routes—i.v., intrapleural, i.p. and incisional—with varying degrees of pain relief [15]. The effect of i.v. administration of local anaesthetics on postoperative pain is controversial, but probably does not significantly affect the postoperative stress

TABLE I. *Effect of extradural or intrathecal local anaesthetics on the endocrine-metabolic response to lower abdominal (gynaecological) surgery, prostatectomy and procedures on the lower extremities. (Data from [14] and [16])*

Type of response	Inhibition or improvement	No important effect	No data
Pituitary	ACTH β-endorphin GH AVP TSH LH and FSH Prolactin	T ₃ and T ₄ Coagulation and fibrinolysis Acute-phase proteins Water and sodium balance	Gastrointestinal peptides Testosterone Estradiol
Adrenal/Renal/ Nervous system	Cortisol Aldosterone Adrenaline Renin Noradrenaline		
Metabolic	Hyperglycemia and glucose tolerance Lipolysis Muscle amino acids Nitrogen balance Oxygen consumption Urinary potassium excretion		

response [3,4,43]. Intrapleural administration of bupivacaine may provide reasonable pain relief after cholecystectomy, kidney surgery, *etc.* [5], but the modifying effect on the stress response and pulmonary function is negligible [35]. I.p. instillation of large doses of bupivacaine has probably no analgesic effect [37,42], and the effect on the stress response is probably insignificant [30,37,42]. Incisional application of local anaesthetics may provide some pain relief [15,40], and preliminary studies of the minor injury produced by inguinal herniotomy suggest some modification of the stress response [40]. However, one should not expect any important modification after major surgical injury.

Regional anaesthesia

The effects of regional anaesthesia (extradural or intrathecal) on the endocrine metabolic response have been reviewed in detail recently [14, 16] and will only be summarized here (table I). Most studies in which a pronounced inhibitory effect has been observed involved operations such as hysterectomy, vaginal surgery, inguinal herniotomy, minor orthopaedic procedures, prostatectomy and hip replacement. In contrast to these studies of operations on the *lower* part of the body, more than 20 studies of extradural analgesia and the stress response to procedures in the upper abdomen and thorax have failed to show a similarly pronounced inhibitory effect. However,

a large variation has been found in the effect of regional anaesthesia on specific endocrine and metabolic changes after upper laparotomy. Unfortunately, interpretation is hindered by lack of control of the degree of sensory block, information on the amount of local anaesthetic administered, degree of pain relief *etc.* [14,16]. Despite these flaws in methodology, it seems valid to conclude that neural block, as produced by extradural analgesia, is less efficient in decreasing the surgical stress response to upper abdominal and thoracic procedures than in decreasing the response to lower body operations. Possible explanations for this are:

- (1) Unblocked vagal afferents (but experimental and clinical studies suggest that these are unimportant [14]).
- (2) Unblocked phrenic afferents. No information is available.
- (3) Insufficient afferent and efferent sympathetic blockade. The addition of a coeliac plexus block has been shown to decrease the stress response further during extradural analgesia [14], and intraoperative splanchnic nerve block decreased several responses during gastrectomy [39]. However, the degree of sympathetic block during regional anaesthesia is under debate [8], and interpretation of the available studies therefore becomes difficult.
- (4) Insufficient afferent somatic block. This is probably the main explanation for the lack of

important effects of extradural local anaesthetics on the stress response to upper abdominal surgery. Studies using evoked potentials have demonstrated that the afferent block is insufficient during thoracic extradural analgesia with conventional doses of bupivacaine [20]. This discrepancy in efficacy between a thoracic extradural and lumbar extradural block is easily understandable, since the amount of local anaesthetic administered during a thoracic extradural technique is less than 50% of that used during a lumbar technique.

(5) The role of unblocked pelvic parasympathetic afferents is unknown.

(6) Potentiating humoral release mechanisms and increased heat loss may also contribute to the decreased effect of regional anaesthesia during major (and long) operations.

The effect of continuous intrathecal block during major procedures has not been studied, but such a block may be expected to be more efficient in decreasing the surgical stress response.

The effect of a pure somatic block with bilateral intercostal nerve block has been addressed in one study. There was no effect on the plasma cortisol response and only a slight inhibitory effect on the glucose response [24]. The effect of continuous paravertebral block on the surgical stress response to upper laparotomy has not been studied, but no major effect would be expected. The administration of 0.5% bupivacaine 5 ml h⁻¹ only provided a moderate degree of pain relief [2].

Thus studies published during the past 2 years have not provided much new information on the inhibitory effect of different regimens of central neural block on the surgical stress response, and further studies should focus on the effect of a more intense block by continuous intrathecal local anaesthetic administration or even combined extradural and intrathecal administration.

Spinal opioids

The effect of extradural or intrathecal opioid administration on the surgical stress response has been reviewed in detail [14,16]. There is general agreement that, despite reasonably good postoperative pain relief, these techniques have no major effect on the surgical stress response, although occasionally an inhibition of some stress parameters has been demonstrated. These studies have therefore emphasized that pain relief *per se* does not necessarily lead to a decrease in the surgical stress response.

Spinal α -adrenergic agonists

The intrathecal or extradural administration of α -adrenergic agonists has been shown experimentally to modulate spinal nociceptive processing [44] and some preliminary clinical studies have shown a small or moderate effect on postoperative pain, or a potentiating effect on local anaesthetic action [21,26]. In a study comparing extradural clonidine 150 μ g with extradural morphine 4 mg after hysterectomy, an almost similar, moderate effect on postoperative pain was obtained, but only a slight modulatory effect on the surgical stress response [21]. No studies are available on the combined effect of extradural clonidine and morphine.

Systemic opioids

The moderate degree of pain relief produced after major procedures by conventional doses of intermittent or continuous opioids has only a negligible effect on the surgical stress response [14,16]. In a study using patient-controlled administration of fentanyl after cholecystectomy, no important effect could be demonstrated on plasma catecholamine or glucose response while postoperative cortisol concentrations were moderately diminished, despite very good pain relief [23]. Thus although there are few available data, optimal pain relief by systemic opioid administration cannot be expected to have an important modulatory effect on the surgical stress response. Very large doses of systemic opioids are necessary if a pronounced decrease in the stress response is required [14,17].

Combined analgesic regimens

Since total postoperative pain relief cannot be achieved by a single agent or method without major expenditure on equipment and surveillance systems, or without significant side effects, recent efforts have focused on improving pain relief by combinations of agents. Thus combining extradural local anaesthetics (0.5% bupivacaine 5–8 ml h⁻¹) with morphine 0.5 mg h⁻¹ provides total pain relief even after upper abdominal surgery [9,36]. However, this is at the cost of either lower extremity paralysis [9] or potential respiratory side effects [36]. The use of lower concentrations of local anaesthetics and morphine leads to less good pain relief [2,6,18,19].

Despite total pain relief after upper abdominal surgery with the combined technique, no sig-

nificant effect was observed on the surgical stress response or the impairment in pulmonary function [36]. Similarly, a combination of extradural bupivacaine with morphine and systemic indomethacin led to total pain relief after cholecystectomy [32], but no clinically significant effect on the impairment in pulmonary function, convalescence or the stress response. These studies, therefore, clearly indicate that total pain relief after major surgery does not necessarily lead to an important decrease in the surgical stress response. Again, this is probably the result of incomplete afferent neural block with several fast conducting neural pathways functioning, despite sufficient block of the slow conducting and pain mediating C-fibres [16,20].

Although a combination of analgesic regimens will have a major place in the future treatment of postoperative pain [15], measures to provide concomitant modification of humorally mediated responses and techniques to improve afferent neural block should be explored. In this context the role of the addition of high dose glucocorticoid therapy should be investigated further. The use of intense intraoperative block by a combination of continuous intrathecal and extradural block may be clinically advantageous (Kehlet and colleagues, unpublished observations), probably because of a decrease in the peripheral and central hypersensitivity to pain that occurs after injury [41].

CLINICAL IMPLICATIONS AND SUMMARY

The clinical implications of pain relief and the variable decrease this produces in the surgical stress response are largely unknown. This is because there are surprisingly few data and those that exist only demonstrate minimal beneficial clinical effects on postoperative morbidity parameters other than pain relief. Thus no controlled study has been performed to evaluate the clinical effect of pain relief by inhibition of endogenous algesic substances. This also applies to the systemic administration of opioids, even when sufficient pain relief is obtained by patient-controlled analgesia.

Postoperative pain relief by extradural opioid administration after conventional extradural block with local anaesthetics probably has no major effect on postoperative morbidity (or the stress response) after major abdominal procedures [10,11,28], although one study in high risk

patients has suggested a major decrease in several complications [46]. In contrast, a vast amount of data exist from controlled studies comparing regional anaesthesia with local anaesthetics and general anaesthesia [34]. Cumulated data, mostly from procedures in the lower abdomen, orthopaedic or urological surgery, demonstrate a beneficial effect of regional anaesthesia on postoperative morbidity parameters such as blood loss, thromboembolic complications, pulmonary infection, gastrointestinal motility and postoperative hospital stay [34]. Interestingly, the most pronounced effect on morbidity occurred in procedures where regional anaesthesia with local anaesthetics also most effectively reduced the stress response. However, the important question whether this represents a causal relationship or an incidental event has not been finally answered.

To summarize, analgesia *per se* may not necessarily have an important effect on the surgical stress response, but is highly dependent on the technique used to provide postoperative pain relief. Furthermore, the effect of pain relief *per se* on postoperative morbidity is probably not a major one, unless the technique also concomitantly decreases the surgical stress response. Future studies should continue to describe the role of the various release mechanisms of the surgical stress response and to evaluate modifying techniques, in the hope of further decreasing postoperative morbidity.

REFERENCES

1. Asoh T, Shirasaka C, Uchida I, Tsuji H. Effects of indomethacin on endocrine responses and nitrogen loss after surgery. *Annals of Surgery* 1987; 206: 770-776.
2. Bigler D, Dirkes W, Rosenberg J, Hansen R, Kehlet H. Comparison of paravertebral bupivacaine vs. epidural bupivacaine plus morphine on pain and pulmonary function after cholecystectomy. *Acta Anaesthesiologica Scandinavica* 1989 (in press).
3. Birch K, Jørgensen J, Chrømmer Jørgensen B, Kehlet H. Effect of i.v. lignocaine on pain and the endocrine metabolic responses after surgery. *British Journal of Anaesthesia* 1987; 59: 721-724.
4. Cassuto J, Wallin G, Högström S, Faxén A, Rimbäck G. Inhibition of postoperative pain by continuous low dose intravenous infusion of lidocaine. *Anesthesia and Analgesia* 1985; 64: 971-974.
5. Covino B. Intrapleural regional analgesia. *Anesthesia and Analgesia* 1988; 67: 427-430.
6. Cullen ML, Starren ED, El-Ganzouri A, Logas WG, Ivankovich AD, Economou SG. Continuous epidural infusion for analgesia of major abdominal operations: a randomized prospective double blind study. *Surgery* 1985; 98: 718-728.

7. Frayn KN. Hormonal control of metabolism in trauma and sepsis. *Clinical Endocrinology* 1986; 24: 577-599.
8. Greene NM. A new look at sympathetic denervation during spinal anesthesia. *Anesthesiology* 1986; 65: 137-138.
9. Hjortso N-C, Lund C, Mogensen T, Bigler D, Kehlet H. Epidural morphine improves pain relief and maintains sensory analgesia during continuous epidural bupivacaine after abdominal surgery. *Anesthesia and Analgesia* 1986; 65: 1033-1036.
10. Hjortso N-C, Neumann P, Frøsig F, Andersen T, Lindhard A, Rogon E, Kehlet H. A controlled study on the effect of the epidural analgesia with local anaesthetics and morphine on morbidity after abdominal surgery. *Acta Anaesthesiologica Scandinavica* 1985; 29: 790-794.
11. Jayr C, Mollie A, Bourgain JL, Alarcon J, Masselot J, Lasser P, Denjean A, Truffa-Bachi J, Henry-Amar M. Postoperative pulmonary complications: general anesthesia with postoperative parenteral morphine compared with epidural analgesia. *Surgery* 1988; 104: 57-63.
12. Johnson DJ, Pressler NM, Smith RJ, Brooks DC, Hulton NR, Colpoys MF, Wilmore DW. Hypothermic anesthesia attenuates postoperative proteolysis. *Annals of Surgery* 1986; 204: 419-429.
13. Kehlet H. The stress response to anaesthesia and surgery: release mechanisms and modifying factors. *Clinics in Anaesthesiology* 1984; 2: 315-339.
14. Kehlet H. Modification of responses to surgery by neural blockade: clinical implications. In: Cousins MJ, Bridenbaugh PO, eds. *Neural Blockade in Clinical Anesthesia and Management of Pain*, 2nd edn. Philadelphia: J.B. Lippincott, 1987; 145-188.
15. Kehlet H. Management of postoperative pain. In: Wilmore O, Brennan M, Meakins JL, eds. *Pre- and Postoperative Care*. New York: Scientific American Inc., 1989 (in press).
16. Kehlet H. The stress response to surgery: release mechanism and the role of pain relief. *Acta Chirurgica Scandinavica* 1988; (Suppl. 550): 22-28.
17. Kehlet H, Schulze S. Modification of the general response to injury—pharmacological and clinical aspects. In: Little RA, Frayn KN, eds. *The Scientific Basis of the Critically Ill*. Manchester: Manchester University Press, 1986; 153-168.
18. Lee A, Simpson D, Whitfield A, Scott DB. Postoperative analgesia by continuous extradural infusion of bupivacaine and diamorphine. *British Journal of Anaesthesia* 1988; 60: 845-850.
19. Logas WG, El-Baz N, El-Ganzouri A, Cullen ML, Starren ED, Faber LP, Ivankovich AD. Continuous thoracic epidural analgesia for postoperative pain relief following thoracotomy: a randomized prospective study. *Anesthesiology* 1987; 67: 787-791.
20. Lund C, Hansen OB, Mogensen T, Kehlet H. Effect of thoracic epidural bupivacaine on somatosensory evoked potentials after dermatomal stimulation. *Anesthesia and Analgesia* 1987; 66: 731-734.
21. Lund C, Qvitzau S, Greulich A, Kehlet H. Effect of extradural clonidine *v.* morphine on pain, stress response and pulmonary function after hysterectomy. *British Journal of Anaesthesia* 1989; (in press).
22. Michie HR, Spriggs DR, Manogue KR, Sherman ML, Revhaug A, O'Dwyer ST, Arthur K, Dinarello CA, Cerami A, Wolff SM, Kufe DW, Wilmore DW. Tumour necrosis factor and endotoxin induce similar metabolic responses in human beings. *Surgery* 1988; 104: 280-286.
23. Møller IV, Dinesen K, Søndergaard S, Knigge U, Kehlet H. Effect of patient-controlled analgesia on plasma catecholamine, cortisol and glucose concentrations after cholecystectomy. *British Journal of Anaesthesia* 1988; 61: 160-164.
24. Pither CE, Bridenbaugh LD, Reynolds F. Preoperative intercostal nerve block: Effect on the endocrine metabolic response to surgery. *British Journal of Anaesthesia* 1988; 60: 730-732.
25. Pomposelle JJ, Flores EA, Bistrrian BR. Role of biochemical mediators in clinical nutrition and surgical metabolism. *Journal of Parenteral and Enteral Nutrition* 1988; 12: 212-218.
26. Racle JP, Benkhadre A, Poy JY, Gleizal B. Prolongation of isobaric bupivacaine spinal anesthesia with epinephrine and clonidine for hip surgery in the elderly. *Anesthesia and Analgesia* 1987; 66: 442-446.
27. Raja SN, Meyer RA, Cambell JN. Peripheral mechanisms of somatic pain. *Anesthesiology* 1988; 68: 571-590.
28. Rawal N, Sjöström U, Christofferson, I, Dahlström B, Arvill A, Rydman H. Comparison of intramuscular and epidural morphine for postoperative analgesia in the grossly obese: influence on postoperative ambulation and pulmonary function. *Anesthesia and Analgesia* 1984; 63: 583-592.
29. Revhaug A, Michie HR, Manson JM, Watters JM, Dinarello CA, Wolff SM, Wilmore DW. Inhibition of cyclo-oxygenase attenuates the metabolic response to endotoxin in humans. *Archives of Surgery* 1988; 123: 162-170.
30. Rimbäck G, Cassuto J, Faxén A, Höglström, S, Wallin G, Tollesson PO. Effect of intraabdominal bupivacaine instillation on postoperative colonic motility. *Gut* 1986; 27: 170-175.
31. Schulze S, Drenck NE, Hjortso E, Kehlet H. Influence of combined neural blockade, H-1 and H-2 receptor and serotonin-2 receptor blockade, indomethacin and tranexamic acid on leucocyte, temperature and acute phase protein response to surgery. *Acta Chirurgica Scandinavica* 1988; 154: 329-333.
32. Schulze S, Roikjaer O, Hasselstrøm L, Jensen NH, Kehlet H. Epidural bupivacaine and morphine plus systemic indomethacin eliminates pain, but not systemic response and convalescence after cholecystectomy. *Surgery* 1988; 103: 321-327.
33. Schulze S, Schierbeck J, Sparso BH, Bisgaard M, Kehlet H. Influence of neural blockade and indomethacin on leucocyte, temperature and acute phase protein response to surgery. *Acta Chirurgica Scandinavica* 1987; 153: 255-259.
34. Scott NB, Kehlet H. Regional anaesthesia and surgical morbidity. *British Journal of Surgery* 1988; 75: 299-304.
35. Scott NB, Mogensen T, Bigler D, Kehlet H. Comparison of continuous intrapleural vs. epidural 0.5% bupivacaine on pain, metabolic response and pulmonary function following cholecystectomy. *Acta Anaesthesiologica Scandinavica* 1989; (in press).
36. Scott NB, Mogensen T, Bigler D, Lund C, Kehlet H. Continuous thoracic extradural 0.5% bupivacaine with or without morphine: effect on quality of blockade, lung function and the surgical stress response. *British Journal of Anaesthesia* 1989; 62: 253-257.

37. Scott NB, Mogensen T, Greulich A, Hjortso N-C, Kehlet H. No effect of continuous i.p. infusion of bupivacaine on postoperative analgesia, pulmonary function and the stress response to surgery. *British Journal of Anaesthesia* 1988; **61**: 165–168.
38. Shaw JHF, Wolfe RR. Metabolic intervention in surgical patients. *Annals of Surgery* 1988; **207**: 274–282.
39. Shirasaka C, Tsuji H, Asoh T, Takiushi Y. Role of the splanchnic nerves in the endocrine and metabolic response to abdominal surgery. *British Journal of Surgery* 1986; **73**: 142–145.
40. Sinclair R, Cassuto J, Högström S, Lindén I, Faxén A, Hedner T, Ekman R. Tropical anesthesia with lidocaine aerosol in the control of postoperative pain. *Anesthesiology* 1988; **68**: 895–901.
41. Wall PD. The prevention of postoperative pain. *Pain* 1988; **33**: 289–290.
42. Wallin G, Cassuto J, Högström S, Hedner T. Influence of intraperitoneal anaesthesia on pain and the sympatho-adrenal response to abdominal surgery. *Acta Anaesthesiologica Scandinavica* 1988; **32**: 553–558.
43. Wallin G, Cassuto J, Högström S, Lindén I, Faxén A, Rimbäck G, Hedner T. Effects of lidocaine infusion on the sympathetic response to abdominal surgery. *Anesthesia and Analgesia* 1987; **66**: 1008–1013.
44. Yaksh TL. Pharmacology of spinal adrenergic systems which modulates spinal nociceptive processing. *Pharmacology, Biochemistry & Behaviour* 1985; **22**: 845–858.
45. Yaksh TL, Hammond DL. Peripheral and central substrates involved in the rostral transmission of nociceptive information. *Pain* 1982; **13**: 1–85.
46. Yeager MP, Glass DD, Neff RK, Brinck-Johnsen T. Epidural anesthesia and analgesia in high risk surgical patients. *Anesthesiology* 1987; **66**: 729–736.