Surgery induced immunosuppression

Article *in* The surgeon: journal of the Royal Colleges of Surgeons of Edinburgh and Ireland · February 2011

DOI: 10.1016/j.surge.2010.07.011 · Source: PubMed

5 authors, including:

Thomas Hughes
University of Leeds
116 PUBLICATIONS **1,325** CITATIONS

SEE PROFILE

available at www.sciencedirect.com

The Surgeon, Journal of the Royal Colleges of Surgeons of Edinburgh and Ireland

www.thesurgeon.net

Review

Surgery induced immunosuppression

Brian V. Hogan [a,*], Mark B. Peter [a], Hrishikesh G. Shenoy [a], Kieran Horgan [a], Thomas A. Hughes [b]

[a] Department of Surgery, Leeds General Infirmary, Great George Street, Leeds, LS1 3EX, United Kingdom
[b] Leeds Institute of Molecular Medicine, St. James's University Hospital, Leeds, LS9 7TF, United Kingdom

ARTICLE INFO

Article history:
Received 27 March 2010
Received in revised form
22 July 2010
Accepted 25 July 2010
Available online 16 September 2010

Keywords:
Surgery
Immunity
Post-operative
Infection
Metastases

ABSTRACT

Surgery and anaesthesia result in a variety of metabolic and endocrine responses, which result in a generalised state of immunosuppression in the immediate post-operative period. Surgery induced immunosuppression has been implicated in the development of post-operative septic complications and tumour metastasis formation. In addition the effectiveness of many treatments in the adjuvant setting is dependent on a functioning immune system. By understanding the mechanisms contributing to surgery-induced immunosuppression, surgeons may undertake strategies to minimise its effect and reduce potential short-term and long-term consequences to patients.

Introduction

Surgical operations cause a variety of immunological disturbances. With a few exceptions the overall picture is one of a generalised state of immunosuppression in the post-operative period. It would appear that the degree to which this occurs and its duration are determined in part by the magnitude of the initial surgical insult. The clinical consequences to patients as a result of this suppression are unclear. There are reports in the literature suggesting that it results in an increased incidence of post-operative wound complications and tumour progression. This review examines the effects of surgery and anaesthesia on components of the immune system, the mechanisms by which these effects may be mediated and the clinical implications of such immune disturbance. In addition we discuss strategies and novel therapies that can be used to modulate the immune system during surgery.

Surgery induced immunosuppression

Surgery induced immunosuppression is caused by the effect on the cellular components of the immune system. Surgery and trauma cause an increase in the total number of white blood cells circulating in the body.[1] However when critical individual leucocyte subpopulations are examined it seems that important groups are suppressed in both number and function. Circulating lymphocyte numbers fall peri-operatively[2–4] and the extent and duration of this fall is related to the magnitude of the surgery.[5,6] This reduction in lymphocyte numbers may be accounted for by a decrease in the lymphocyte proliferation rate[7,8] or as a result of a redistribution of lymphocytes from the peripheral blood to the body compartments.[9] When lymphocytes have been differentiated into T and B cells it apparent that T lymphocytes are most affected,

* *Corresponding author*. Tel.: +44 113 3923325; fax: +44 113 3922250.
E-mail address: bvhogan@yahoo.co.uk (B.V. Hogan).

1479-666X/$ – see front matter
doi:10.1016/j.surge.2010.07.011

with B lymphocyte numbers changing little.[2] As well as a decrease in T lymphocyte numbers surgery also causes a shift in the balance between the immune-suppressive regulatory T lymphocytes and the immune promoting helper T and cytotoxic T cells[3]. This shift results in a predominance of T regulatory cells in the post-operative period. The immunosuppressive effect of this imbalance may be observed up to two weeks post-operatively.[3] In addition numerous studies have observed impaired T cell function as a result of surgery.[10,11] Reports suggest that this, again, may be proportional to the extent of the surgery, with laparoscopic surgery having a less pronounced effect than conventional open surgery.[12,13]

Natural Killer (NK) cell numbers and function are also affected by surgery. Cristaldi et al reported a fall in NK cell numbers that persisted for up to thirty days post-operatively following open cholecystectomy.[5] Suppression of NK cell numbers also occurs following other forms of surgery.[2,6] Laparoscopic colorectal surgery allows for greater preservation of NK cell numbers than conventional open surgery.[14] Interestingly NK cell activation and cytotoxicity increase following the administration of pre-medication to patients, and with the induction of anaesthesia. However, this is followed by a rapid and significant decrease in activity post-operatively.[15] Suppression of NK cell cytotoxicity may persist for up to ten days[16] and, again, appears to relate to the severity of the surgery although the type of anaesthesia may also have a role.[17]

Other components of the cell-mediated immune system are also negatively affected by surgery and anaesthesia. While most authors report an increase in neutrophil numbers post-operatively,[1,18,19] many also show that their phagocytic function is inhibited as a result of surgery.[20–23] The motility of neutrophils is reduced as a result of surgery[24] as is their production of hypochlorous acid, an important anti-microbial.[25] Anaesthesia and surgery also impair monocyte and macrophage functions, including chemotaxis and phagocytosis.[26,27] This loss of function may relate to the observed loss of surface HLA-DR expression on these cell types,[23,28,29] since HLA-DR is an important component of the antigen recognition mechanism. Again conventional open surgery has a more profound effect than less invasive laparoscopic surgery.[29–31] The reasons for this are better understood when we examine the mechanisms behind surgery induced immunosuppression.

Mechanisms of immunosuppression

Immune changes occurring peri-operatively are primarily as a result of surgical trauma and subsequent neuroendocrine responses. Activation of the hypothalamic–pituitary–adrenal axis (HPA) is the key response to stress and plays a central role in mediating the effect of surgery on the immune system.[32,33] Peri-operative stresses both physical and psychological result in the increased production of adrenocorticotropic hormone (ACTH) from the pituitary gland, and subsequent release of glucocorticoids such as cortisol from the adrenal gland. This increase in ACTH and glucocorticoid production may persist for several days following surgery and is proportional to the severity of the surgical stress. Glucocorticoids are known to suppress cell mediated immunity.[34,35] Cortisol prevents proliferation of T lymphocytes by rendering interleukin-2 producing T cells unresponsive to IL-1 and unable to produce T cell growth factor.[36] Glucocorticoids not only reduce T cell proliferation but are also known to increase apoptosis of immature T cells leading to atrophy of the cortical area of the thymus gland.[37] Glucocorticoid induced lymphocytopenia may also be partly due to a redistribution of lymphocytes out of the circulation into other body compartments.[38] It is uncertain where the lymphocytes migrate to, with one report suggesting that they may be redistributed from the spleen and peripheral blood to the lymphatic tissues.[9]

More recent work suggests that the immunosuppressive effect of glucocorticoids as seen in the peri-operative period may be mediated through their effect on the expression of certain target genes in leucocytes. Glucocorticoids increase expression of a number of anti-inflammatory genes resulting in increased production of lipocortin 1[39] and secretory leucocyte proteinase inhibitor.[40] Lipocortin 1 inhibits production of phospholipase A2 a regulator in the production of pro-inflammatory prostaglandins and leucotrienes. Secretory leukocyte protease inhibitor is active against neutrophil elastase and cathespin G, neutrophil proteases involved in inflammation and phagocytosis.[41] Glucocorticoid inhibition of gene expression in leucocytes, results in decreased production of many pro-inflammatory cytokines including IL-1, IL-2, IL-6, IL-11, IL-13 and TNF-α.[42–44] It is now known that cytokines IL-1 and IL-6 stimulate the HPAA resulting in increased production of glucocorticoids from the adrenal gland.[45,46] This is believed to be mediated through the release of corticotrophin releasing hormone CRH from the hypothalamus[47] and may represent an important negative feedback effect on the immunosuppressive actions of the HPA axis.

Activation of the sympathetic nervous system during surgery also has a profound effect on the immune system. The immune organs or lymphoid organs are innervated with sympathetic nerve fibres and can be directly stimulated by the sympathetic nervous system as part of the "flight of fight response".[48] The subsequent release of cathecholamines; adrenaline and noradrenaline from the nerve terminals has predominantly immunosuppressive effects. These effects are mediated through the interaction of cathecholamines with adrenergic receptors present on the surface of immune cells. These adrenergic binding sites have been identified on many immune cell subtypes and are predominately of the β2 subtype.[49,50] Adrenaline released as a result of surgical stress activates β2 receptors on T lymphocytes. This inhibits T cell proliferation by decreasing IL-2 expression and secretion[51,52]. In vitro studies suggest that exposure of NK cells to a β2 agonist such as adrenaline also reduces NK cell activity.[53,54] Neutrophils are also inhibited by exposure to adrenaline. Neutrophil production of anti-microbial superoxide radicals is reduced[20,55] as is their ability to adhere to vascular endothelium.[56] In contrast however, other reports suggest that β2 stimulation results in increased cell motility and increased accumulation of neutrophils at sites of inflammation.[49]

Recently, along with immune suppression caused by surgical stress, numerous studies have shown that anaesthetics and analgesic agents used peri-operatively may have a direct toxic effect on components of the immune system. Propofol, a commonly used intra-venous anaesthetic agent,

inhibits neutrophil and macrophage chemotaxis and phagocytosis.[26,27] However propofol has also been shown to have a less pronounced effect on circulating lymphocyte numbers than other anaesthetic agents such as sevoflurane.[57] The mode of anaesthetic administration may also affect the degree of immunosuppression; for example, the use of spinal anaesthesia results in better preservation of T cell proliferation than general anaesthesia for prostate surgery.[58] Opioids are commonly used analgesic agents in surgery and are known to have immunosuppressive effects. Morphine is known to suppress a variety of immune functions including NK cell activity,[59] T lymphocyte proliferation[60] as well as neutrophil and macrophage phagocytic activity.[61] These immunosuppressive effects are mediated indirectly by opiate activation of the HPA axis[62] and also through activation of the sympathetic nervous system.[63] In addition opioid receptors are found on many subtypes of immune cells allowing for a direct effect of opiates on the immune system.[64]

Clinical consequences of surgery induced immunosuppression

The clinical consequences of peri-operative immunosuppression were documented as far back as 1911 when Graham reported that ether induced a reduction in bacterial phagocytosis increasing the risk of post-operative septic complications.[65] Gaylord in 1916 showed an increased frequency of metastases from mammary carcinoma in mice following anaesthesia and blood loss.[66] More recent studies also suggest that the immunological effects of surgery have both immediate and delayed consequences for patients. In the oncological setting the effect of surgery on NK cell number and activity has been linked to an increased risk of mortality and cancer recurrence in patients with colorectal,[67] breast,[68] head and neck[69] and lung cancers.[70] Tartter showed that a low level of NK cytotoxicity in the immediate pre-operative period, was an independent predictor of recurrence in colorectal carcinoma.[67] In the post-operative period reduced NK activity was an independent predictor of survival in patients with non-small cell lung carcinoma.[70] In all forms of surgery, oncological and otherwise, peri-operative immunosuppression can result in more immediate consequences for patients including delayed wound healing and other septic events. Wakefield et al showed that a peri-operative drop in HLA-DR expressing monocytes was associated with the occurrence of wound complications and respiratory infections post-operatively.[71] Duignan showed that impairment of neutrophil chemotaxis as a result of surgery was also associated with the development of septic complications.[72]

Measures to reduce immunosuppressive effect of surgery

An understanding of the mechanisms by which surgery induces immunosuppression allows for the implementation of certain measures to minimise negative consequences to patients. Efforts to reduce the immunosuppressive effects of surgery and anaesthesia must be initiated in the pre-operative period. These efforts should be focussed on minimising the neuroendocrine stress response associated with surgery. Effective emotional support and counselling as well as appropriate pre-medication use may help reduce pre-operative psychological stress. Physical stressors associated with surgery such as dehydration and hypothermia also contribute to activation of the HPA axis and thereby subsequent immunosuppression. Ensuring adequate tissue perfusion is essential as are measures to maintain core body temperature such as fluid warmers and external body warming devices. A key issue in minimising the immunosuppressive effect of surgery is adequate pain control throughout the surgical experience. Epidural analgesia can be considered in suitable individuals as a means of reducing stress-induced immunosuppression in patients undergoing major abdominal surgery.[73] While opiates are known to have direct suppressive effects on immune cell activity, it has also been shown that analgesic doses of morphine significantly reduce the tumour promoting effects of surgery.[74] The reason for this contradictatory effect is not understood. Tramadol, a synthetic opioid, has less inhibitory effects on phagocytic cells than conventional opiates[75] while buprenorphine appears to exhibit a neutral effect on the immune system.[76] Non-steroidal anti-inflammatory drugs (NSAIDs), while possessing anti-inflammatory properties are also effective analgesics and antipyretics. They also reduce prostaglandin E2 induced immunosuppression and their use is therefore considered appropriate in minimising the immunosuppressive effect of surgery.[77] Other immunoprotective measures that may be employed include minimising the use of blood transfusion products[78] and ensuring the nutritional integrity of the patients particularly in the post-operative setting.

The development of minimally invasive surgery has allowed major changes in surgical practice, especially because it limits surgical trauma. This results in better preservation of lymphocyte subpopulations, neutrophil function and cell mediated immunity than conventional open surgery.[25,79,80] This preservation of the immune system may contribute to the reduced post-operative complication rate and shorter hospital stay experienced by patients undergoing laparoscopic procedures.[81,82] Future development of minimal access surgery may be an important step in minimising surgery induced immunosuppression and its potential complications.

The role of immunomodulators in the surgical setting has attracted much attention in recent years. The majority of work has focussed on immunosuppressants, particularly in the organ transplant setting. However, there has also been considerable interest in the use of immunostimulants to minimise the immunosuppressing effect of surgery and reduce the risk of metastatic spread. In this context, numerous animal studies have shown anti-neoplastic effects of IL-12.[83,84] This effect is thought to be mediated through increased production of IFN-γ[85,86] and upregulation of cell mediated immunity specifically through T cells.[87] Research to date has shown limited success in treating advanced or recurrent disease.[88,89] However a recent study showed that the prophylactic use of IL-12 peri-operatively abolished the metastases-promoting effects of surgery in a murine model. In this case an IL-12 dependent increase in NK cell numbers was thought to be responsible.[90] However, toxicities associated with IL-12 administration have thus far limited its clinical use. Other

animal studies have shown that the peri-operative administration of immune promoting cytokines such as IFN-α can also inhibit the development of post-operative metastasis and increase survival rates.[91,92] In the clinical setting there is evidence that the administration of IL-2 pre-operatively stimulates cell mediated immunity and improves survival for patients with colorectal and pancreatic cancer.[93–95] Active immunotherapy in the form of a vaccine was initially shown to improve survival following resection of disseminated melanoma.[96] This vaccine was prepared from allogeneic melanoma cell lines grown in culture. However, subsequent phase III trials did not support these initial positive findings and use of the vaccine was discontinued. While results from the clinical use of active immunomodulators are limited and varied it would appear that that their potential role should be targeted in the peri-operative setting to counteract the immunosuppressive effects of surgery and minimise the risk of metastatic development from minimal residual disease following resection of the primary tumour bulk.

Conclusion

Surgery induced immunosuppression has considerable implications for patients. It is associated with impaired wound healing and delayed post-operative recovery. Its implications for cancer patients are more profound, being associated with an increased incidence of cancer recurrence and reduced survival. In addition the effectiveness of many adjuvant treatments is dependent on the preservation of immune integrity in patients during and following resection of the primary tumour. An understanding of the neuroendocrine mechanisms contributing to this process may allow for the implementation of strategies to minimise peri-operative immunosuppression and its consequences for patients.

REFERENCES

1. Redmond HP, Watson W, Hougton T, Condron C, Watson RG, Hayes DB. Immune function in patients undergoing open vs laparoscopic cholecystectomy. *Arch Surg* 1994;**129**(12):1240–6.
2. Lennard TW, Shenton BK, Borzotta A, Donnelly PK, White M, Gerrie LM, et al. The influence of surgical operations on components of the human immune system. *Br J Surg* 1985;**72**(10):771–6.
3. Ogawa K, Hirai M, Katsube T, Murayama M, Hamaguchi K, Shimakawa T, et al. Suppression of cellular immunity by surgical stress. *Surgery* 2000;**127**(3):329–36.
4. Vallina VL, Velasco JM. The influence of laparoscopy on lymphocyte subpopulations in the surgical patient. *Surg Endosc* 1996;**10**(5):481–4.
5. Cristaldi M, Rovati M, Elli M, Gerlinzani S, Lesma A, Balzarotti L, et al. Lymphocytic subpopulation changes after open and laparoscopic cholecystectomy: a prospective and comparative study on 38 patients. *Surg Laparosc Endosc* 1997;**7**(3):255–61.
6. Leaver HA, Craig SR, Yap PL, Walker WS. Lymphocyte responses following open and minimally invasive thoracic surgery. *Eur J Clin Invest* 2000;**30**(3):230–8.
7. Salo M, Eskola J, Nikoskelainen J. T and B lymphocyte function in anaesthetists. *Acta Anaesthesiol Scand* 1984;**28**(3):292–5.
8. Ferrero E, Ferrero ME, Marni A, Zocchi MR, Stella L, Rugarli C, et al. In vitro effects of halothane on lymphocytes. *Eur J Anaesthesiol* 1986;**3**(4):321–30.
9. Toft P, Lillevang ST, Tønnesen E, Svendsen P, Höhndorf K. Redistribution of lymphocytes following *E. coli* sepsis. *Scand J Immunol* 1993;**38**(6):541–5.
10. Shafir M, Bekesi JG, Papatestas A, Slater G, Aufses Jr AH. Preoperative and postoperative immunological evaluation of patients with colorectal cancer. *Cancer* 1980;**46**(4):700–5.
11. Brune IB, Wilke W, Hensler T, Holzmann B, Siewert JR. Downregulation of T helper type 1 immune response and altered pro-inflammatory and anti-inflammatory T cell cytokine balance following conventional but not laparoscopic surgery. *Am J Surg* 1999;**177**(1):55–60.
12. Decker D, Lindemann C, Springer W, Low A, Hirner A, von Ruecker A. Endoscopic vs conventional hernia repair from an immunologic point of view. *Surg Endosc* 1999;**13**(4):335–9.
13. Ishikawa M, Nishioka M, Hanaki N, Miyauchi T, Kashiwagi Y, Ioki H, et al. Perioperative immune responses in cancer patients undergoing digestive surgeries. *World J Surg Oncol* 2009;**7**:7.
14. Wichmann MW, Hüttl TP, Winter H, Spelsberg F, Angele MK, Heiss MM, et al. Immunological effects of laparoscopic vs open colorectal surgery: a prospective clinical study. *Arch Surg* 2005;**140**(7):692–7.
15. Tonnesen E. Immunological aspects of anaesthesia and surgery—with special reference to NK cells. *Dan Med Bull* 1989;**36**(3):263–81.
16. Lukomska B, Olszewski WL, Engeset A, Kolstad P. The effect of surgery and chemotherapy on blood NK cell activity in patients with ovarian cancer. *Cancer* 1983;**51**(3):465–9.
17. Koltun WA, McKenna KJ, Rung G. Awake epidural anesthesia is associated with improved natural killer cell cytotoxicity and a reduced stress response. *Am J Surg* 1996;**171**(1):68–72. discussion 72-3.
18. Slade MS, Simmons L, Yunis E, Greenberg LJ. Immunodepression after major surgery in normal patients. *Surgery* 1975;**78**(3):363–72.
19. van Dijk WC, Verbrugh HA, van Rijswijk RE, Vos A, Verhoef J. Neutrophil function, serum opsonic activity, and delayed hypersensitivity in surgical patients. *Surgery* 1982;**92**(1):21–9.
20. Nakagawara M, Takeshige K, Takamatsu J, Takahashi S, Yoshitake J, Minakami S. Inhibition of superoxide production and Ca^{2+} mobilization in human neutrophils by halothane, enflurane, and isoflurane. *Anesthesiology* 1986;**64**(1):4–12.
21. Fröhlich D, Rothe G, Schwall B, Schmid P, Schmitz G, Taeger K, et al. Effects of volatile anaesthetics on human neutrophil oxidative response to the bacterial peptide FMLP. *Br J Anaesth* 1997;**78**(6):718–23.
22. Welch WD. Halothane reversibly inhibits human neutrophil bacterial killing. *Anesthesiology* 1981;**55**(6):650–4.
23. Kawasaki T, Ogata M, Kawasaki C, Okamoto K, Sata T. Effects of epidural anaesthesia on surgical stress-induced immunosuppression during upper abdominal surgery. *Br J Anaesth* 2007;**98**(2):196–203.
24. Moudgil GC, Pandya AR, Ludlow DJ. Influence of anaesthesia and surgery on neutrophil chemotaxis. *Can Anaesth Soc J* 1981;**28**(3):232–8.
25. Carey PD, Wakefield CH, Thayeb A, Monson JR, Darzi A, Guillou PJ. Effects of minimally invasive surgery on hypochlorous acid production by neutrophils. *Br J Surg* 1994;**81**(4):557–60.
26. Wu GJ, Tai YT, Chen TL, Lin LL, Ueng YF, Chen RM. Propofol specifically inhibits mitochondrial membrane potential but not complex I NADH dehydrogenase activity, thus reducing cellular ATP biosynthesis and migration of macrophages. *Ann N Y Acad Sci* 2005;**1042**:168–76.
27. Chen RM, Wu CH, Chang HC, Wu GJ, Lin YL, Sheu JR. Propofol suppresses macrophage functions and modulates

mitochondrial membrane potential and cellular adenosine triphosphate synthesis. *Anesthesiology* 2003;**98**(5):1178–85.
28. Sietses C, Wiezer MJ, Eijsbouts QA, Beelen RH, van Leeuwen PA, von Blomberg BM. A prospective randomized study of the systemic immune response after laparoscopic and conventional Nissen fundoplication. *Surgery* 1999;**126**(1):5–9.
29. Brune IB, Wilke W, Hensler T, Feussner H, Holzmann B, Siewert JR. Normal T lymphocyte and monocyte function after minimally invasive surgery. *Surg Endosc* 1998;**12**(8):1020–4.
30. Kloosterman T, von Blomberg BM, Borgstein P, Cuesta MA, Scheper RJ, Meijer S. Unimpaired immune functions after laparoscopic cholecystectomy. *Surgery* 1994;**115**(4):424–8.
31. Novitsky YW, Czerniach DR, Kaban GK, Bergner A, Gallagher KA, Perugini RA, et al. Immunologic effects of hand-assisted surgery on peritoneal macrophages: comparison to open and standard laparoscopic approaches. *Surgery* 2006;**139**(1):39–45.
32. Chrousos GP. The hypothalamic–pituitary–adrenal axis and immune-mediated inflammation. *N Engl J Med* 1995;**332**(20):1351–62.
33. Kennedy BC, Hall GM. Neuroendocrine and inflammatory aspects of surgery: do they affect outcome? *Acta Anaesthesiol Belg* 1999;**50**(4):205–9.
34. Larsson EL. Cyclosporin A and dexamethasone suppress T cell responses by selectively acting at distinct sites of the triggering process. *J Immunol* 1980;**124**(6):2828–33.
35. Arya SK, Wong-Staal F, Gallo RC. Dexamethasone-mediated inhibition of human T cell growth factor and gamma-interferon messenger RNA. *J Immunol* 1984;**133**(1):273–6.
36. Palacios R, Sugawara I. Hydrocortisone abrogates proliferation of T cells in autologous mixed lymphocyte reaction by rendering the interleukin-2 Producer T cells unresponsive to interleukin-1 and unable to synthesize the T-cell growth factor. *Scand J Immunol* 1982;**15**(1):25–31.
37. Nieto MA, González A, Gambón F, Díaz-Espada F, López-Rivas A. Apoptosis in human thymocytes after treatment with glucocorticoids. *Clin Exp Immunol* 1992;**88**(2):341–4.
38. Dhabhar FS, Miller AH, McEwen BS, Spencer RL. Stress-induced changes in blood leukocyte distribution. Role of adrenal steroid hormones. *J Immunol* 1996;**157**(4):1638–44.
39. Flower RJ. Eleventh Gaddum memorial lecture. Lipocortin and the mechanism of action of the glucocorticoids. *Br J Pharmacol* 1988;**94**(4):987–1015.
40. Sallenave JM, Shulmann J, Crossley J, Jordana M, Gauldie J. Regulation of secretory leukocyte proteinase inhibitor (SLPI) and elastase-specific inhibitor (ESI/elafin) in human airway epithelial cells by cytokines and neutrophilic enzymes. *Am J Respir Cell Mol Biol* 1994;**11**(6):733–41.
41. Mulligan MS, Lentsch AB, Huber-Lang M, Guo RF, Sarma V, Wright CD. Anti-inflammatory effects of mutant forms of secretory leukocyte protease inhibitor. *Am J Pathol* 2000;**156**(3):1033–9.
42. Umland SP, Schleimer RP, Johnston SL. Review of the molecular and cellular mechanisms of action of glucocorticoids for use in asthma. *Pulm Pharmacol Ther* 2002;**15**(1):35–50.
43. Re F, Muzio M, Bertini R, Polentarutti N, Sironi M, Giri JG, et al. The type II "receptor" as a decoy target for interleukin 1 in polymorphonuclear leukocytes: characterization of induction by dexamethasone and ligand binding properties of the released decoy receptor. *J Exp Med* 1994;**179**(2):739–43.
44. Mozo L, Gayo A, Suárez A, Rivas D, Zamorano J, Gutiérrez C. Glucocorticoids inhibit IL-4 and mitogen-induced IL-4R alpha chain expression by different posttranscriptional mechanisms. *J Allergy Clin Immunol* 1998;**102**(6 Pt 1):968–76.
45. Kusnecov AW, Rossi-George A. Potentiation of interleukin-1beta adjuvant effects on the humoral immune response to antigen in adrenalectomized mice. *Neuroimmunomodulation* 2001;**9**(2):109–18.
46. Venihaki M, Dikkes P, Carrigan A, Karalis KP. Corticotropin-releasing hormone regulates IL-6 expression during inflammation. *J Clin Invest* 2001;**108**(8):1159–66.
47. Sapolsky R, Rivier C, Yamamoto G, Plotsky P, Vale W. Interleukin-1 stimulates the secretion of hypothalamic corticotropin-releasing factor. *Science* 1987;**238**(4826):522–4.
48. Panuncio AL, De La Peña S, Gualco G, Reissenweber N. Adrenergic innervation in reactive human lymph nodes. *J Anat* 1999;**194**(Pt 1):143–6.
49. de Coupade C, Gear RW, Dazin PF, Sroussi HY, Green PG, Levine JD. Beta 2-adrenergic receptor regulation of human neutrophil function is sexually dimorphic. *Br J Pharmacol* 2004;**143**(8):1033–41.
50. Elenkov IJ, Wilder RL, Chrousos GP, Vizi ES. The sympathetic nerve–an integrative interface between two supersystems: the brain and the immune system. *Pharmacol Rev* 2000;**52**(4):595–638.
51. Chen D, Rothenberg EV. Interleukin 2 transcription factors as molecular targets of cAMP inhibition: delayed inhibition kinetics and combinatorial transcription roles. *J Exp Med* 1994;**179**(3):931–42.
52. Tamir A, Isakov N. Cyclic AMP inhibits phosphatidylinositol-coupled and -uncoupled mitogenic signals in T lymphocytes. Evidence that cAMP alters PKC-induced transcription regulation of members of the jun and fos family of genes. *J Immunol* 1994;**152**(7):3391–9.
53. Gan X, Zhang L, Solomon GF, Bonavida B. Mechanism of norepinephrine-mediated inhibition of human NK cytotoxic functions: inhibition of cytokine secretion, target binding, and programming for cytotoxicity. *Brain Behav Immun* 2002;**16**(3):227–46.
54. Hellstrand K, Hermodsson S. An immunopharmacological analysis of adrenaline-induced suppression of human natural killer cell cytotoxicity. *Int Arch Allergy Appl Immunol* 1989;**89**(4):334–41.
55. Mirza ZN, Kato M, Kimura H, Tachibana A, Fujiu T, Suzuki M, et al. Fenoterol inhibits superoxide anion generation by human polymorphonuclear leukocytes via beta-adrenoceptor-dependent and -independent mechanisms. *Ann Allergy Asthma Immunol* 2002;**88**(5):494–500.
56. Bloemen PG, van den Tweel MC, Henricks PA, Engels F, Kester MH, van de Loo PG, et al. Increased cAMP levels in stimulated neutrophils inhibit their adhesion to human bronchial epithelial cells. *Am J Physiol* 1997;**272**(4 Pt 1):L580–7.
57. Kitamura T, Ohno N, Bougaki M, Ogawa M, Yamada Y. [Comparison of the effects of sevoflurane and propofol on changes in leukocyte-count induced by surgical stress]. *Masui* 2008;**57**(8):968–72.
58. Le Cras AE, Galley HF, Webster NR. Spinal but not general anesthesia increases the ratio of T helper 1 to T helper 2 cell subsets in patients undergoing transurethral resection of the prostate. *Anesth Analg* 1998;**87**(6):1421–5.
59. Beilin B, Shavit Y, Cohn S, Kedar E. Narcotic-induced suppression of natural killer cell activity in ventilated and nonventilated rats. *Clin Immunol Immunopathol* 1992;**64**(2):173–6.
60. Fuchs BA, Pruett SB. Morphine induces apoptosis in murine thymocytes in vivo but not in vitro: involvement of both opiate and glucocorticoid receptors. *J Pharmacol Exp Ther* 1993;**266**(1):417–23.
61. Eisenstein TK, Hilburger ME. Opioid modulation of immune responses: effects on phagocyte and lymphoid cell populations. *J Neuroimmunol* 1998;**83**(1–2):36–44.
62. Freier DO, Fuchs BA. A mechanism of action for morphine-induced immunosuppression: corticosterone mediates

morphine-induced suppression of natural killer cell activity. *J Pharmacol Exp Ther* 1994;**270**(3):1127–33.
63. Flores LR, Dretchen KL, Bayer BM. Potential role of the autonomic nervous system in the immunosuppressive effects of acute morphine administration. *Eur J Pharmacol* 1996;**318**(2–3):437–46.
64. Carr DJ, DeCosta BR, Kim CH, Jacobson AE, Guarcello V, Rice KC, et al. Opioid receptors on cells of the immune system: evidence for delta- and kappa-classes. *J Endocrinol* 1989;**122**(1):161–8.
65. Graham EA. The influence of ether and ether anaesthesia on bacteriolysis, agglutination, and phagocytosis. *J Infect Dis* 1911;**8**:147–75.
66. Ricci C, Pastukh V, Mozaffari M, Schaffer SW. Insulin withdrawal induces apoptosis via a free radical-mediated mechanism. *Can J Physiol Pharmacol* 2007;**85**(3–4):455–64.
67. Tartter PI, Steinberg B, Barron DM, Martinelli G. The prognostic significance of natural killer cytotoxicity in patients with colorectal cancer. *Arch Surg* 1987;**122**(11):1264–8.
68. Levy SM, Herberman RB, Maluish AM, Schlien B, Lippman M. Prognostic risk assessment in primary breast cancer by behavioral and immunological parameters. *Health Psychol* 1985;**4**(2):99–113.
69. Schantz SP, Brown BW, Lira E, Taylor DL, Beddingfield N. Evidence for the role of natural immunity in the control of metastatic spread of head and neck cancer. *Cancer Immunol Immunother* 1987;**25**(2):141–8.
70. Fujisawa T, Yamaguchi Y. Autologous tumor killing activity as a prognostic factor in primary resected nonsmall cell carcinoma of the lung. *Cancer* 1997;**79**(3):474–81.
71. Wakefield CH, Carey PD, Foulds S, Monson JR, Guillou PJ. Changes in major histocompatibility complex class II expression in monocytes and T cells of patients developing infection after surgery. *Br J Surg* 1993;**80**(2):205–9.
72. Duignan JP, Collins PB, Johnson AH, Bouchier-Hayes D. The association of impaired neutrophil chemotaxis with postoperative surgical sepsis. *Br J Surg* 1986;**73**(3):238–40.
73. Ahlers O, Nachtigall I, Lenze J, Goldmann A, Schulte E, Höhne C, et al. Intraoperative thoracic epidural anaesthesia attenuates stress-induced immunosuppression in patients undergoing major abdominal surgery. *Br J Anaesth* 2008;**101**(6):781–7.
74. Page GG, Blakely WP, Ben-Eliyahu S. Evidence that postoperative pain is a mediator of the tumor-promoting effects of surgery in rats. *Pain* 2001;**90**(1–2):191–9.
75. Beilin B, Grinevich G, Yardeni IZ, Bessler H. Tramadol does not impair the phagocytic capacity of human peripheral blood cells. *Can J Anaesth* 2005;**52**(10):1035–9.
76. Pergolizzi J, Aloisi AM, Dahan A, Filitz J, Langford R, Likar R et al. Current knowledge of buprenorphine and its unique pharmacological profile. Pain Pract.
77. Mahdy AM, Galley HF, Abdel-Wahed MA, el-Korny KF, Sheta SA, Webster NR. Differential modulation of interleukin-6 and interleukin-10 by diclofenac in patients undergoing major surgery. *Br J Anaesth* 2002;**88**(6):797–802.
78. Kendall SJ, Weir J, Aspinall R, Henderson D, Rosson J. Erythrocyte transfusion causes immunosuppression after total hip replacement. *Clin Orthop Relat Res* 2000;(381):145–55.
79. Kehlet H, Nielsen HJ. Impact of laparoscopic surgery on stress responses, immunofunction, and risk of infectious complications. *New Horiz* 1998;**6**(Suppl. 2):S80–8.
80. Bessler M, Whelan RL, Halverson A, Treat MR, Nowygrod R. Is immune function better preserved after laparoscopic versus open colon resection? *Surg Endosc* 1994;**8**(8):881–3.
81. Stewart BT, Stitz RW, Lumley JW. Laparoscopically assisted colorectal surgery in the elderly. *Br J Surg* 1999;**86**(7):938–41.
82. Basse L, Madsen JL, Billesbølle P, Bardram L, Kehlet H. Gastrointestinal transit after laparoscopic versus open colonic resection. *Surg Endosc* 2003;**17**(12):1919–22.
83. Brunda MJ, Luistro L, Warrier RR, Wright RB, Hubbard BR, Murphy M, et al. Antitumor and antimetastatic activity of interleukin 12 against murine tumors. *J Exp Med* 1993;**178**(4):1223–30.
84. Smyth MJ, Taniguchi M, Street SE. The anti-tumor activity of IL-12: mechanisms of innate immunity that are model and dose dependent. *J Immunol* 2000;**165**(5):2665–70.
85. Zou JP, Yamamoto N, Fujii T, Takenaka H, Kobayashi M, Herrmann SH, et al. Systemic administration of rIL-12 induces complete tumor regression and protective immunity: response is correlated with a striking reversal of suppressed IFN-gamma production by anti-tumor T cells. *Int Immunol* 1995;**7**(7):1135–45.
86. Colombo MP, Trinchieri G. Interleukin-12 in anti-tumor immunity and immunotherapy. *Cytokine Growth Factor Rev* 2002;**13**(2):155–68.
87. Kobayashi T, Shiiba K, Satoh M, Hashimoto W, Mizoi T, Matsuno S, et al. Interleukin-12 administration is more effective for preventing metastasis than for inhibiting primary established tumors in a murine model of spontaneous hepatic metastasis. *Surg Today* 2002;**32**(3):236–42.
88. Hurteau JA, Blessing JA, DeCesare SL, Creasman WT. Evaluation of recombinant human interleukin-12 in patients with recurrent or refractory ovarian cancer: a gynecologic oncology group study. *Gynecol Oncol* 2001;**82**(1):7–10.
89. Atkins MB, Robertson MJ, Gordon M, Lotze MT, DeCoste M, DuBois JS, et al. Phase I evaluation of intravenous recombinant human interleukin 12 in patients with advanced malignancies. *Clin Cancer Res* 1997;**3**(3):409–17.
90. Schwartz Y, Avraham R, Benish M, Rosenne E, Ben-Eliyahu S. Prophylactic IL-12 treatment reduces postoperative metastasis: mediation by increased numbers but not cytotoxicity of NK cells. *Breast Cancer Res Treat* 2008;**107**(2):211–23.
91. Dithmar S, Rusciano D, Lynn MJ, Lawson DH, Armstrong CA, Grossniklaus HE. Neoadjuvant interferon alfa-2b treatment in a murine model for metastatic ocular melanoma: a preliminary study. *Arch Ophthalmol* 2000;**118**(8):1085–9.
92. Gallagher WJ, Dubinett SM, Hoover Jr HC, Kradin RL. Efficacy of adjuvant interleukin-2 after excision of BALB/c fibrosarcomas. *Surgery* 1989;**106**(2):120–5.
93. Caprotti R, Brivio F, Fumagalli L, Nobili C, Degrate L, Lissoni P, et al. Free-from-progression period and overall short preoperative immunotherapy with IL-2 increases the survival of pancreatic cancer patients treated with macroscopically radical surgery. *Anticancer Res* 2008;**28**(3B):1951–4.
94. Brivio F, Lissoni P, Alderi G, Barni S, Lavorato F, Fumagalli. Nonalcoholic steatohepatitis. *Oncology* 1996;**53**(4):263–8.
95. Brivio F, Lissoni P, Fumagalli L, Girlando M, Marsili MT, Nespoli A, et al. Pre-operative IL-2 immunoprophylaxis of cancer recurrence: long-term clinical results of a phase II study in radically operable colorectal cancer. *Oncol Rep* 1999;**6**(6):1205–7.
96. Hsueh EC, Essner R, Foshag LJ, Ollila DW, Gammon G, O'Day SJ, et al. Prolonged survival after complete resection of disseminated melanoma and active immunotherapy with a therapeutic cancer vaccine. *J Clin Oncol* 2002;**20**(23):4549–54.