Effects of anaesthesia on the human immune system

John D Hunter

The ability of certain anaesthetic agents to influence the immune response has been recognized for almost 30 years. The purpose of this review is to briefly describe the different components of the immune system and examine the way in which surgery and anaesthesia influence these.

Drugs used for the induction and maintenance of anaesthesia have a profound influence on the major organ systems of the body. It is therefore not surprising that there has been much interest in the effects of anaesthetic agents on the human immune system. Since an appropriate immune response is essential for preventing infection and eliminating tumour cells, factors which compromise the optimal functioning of the host's defence mechanisms may adversely affect the outcome.

While the magnitude of surgical trauma is thought to have a more pronounced effect on the immune response than anaesthesia itself, in-vivo and in-vitro work suggests that anaesthetic agents have a significant immunomodulatory effect.

The potential for anaesthesia to influence the immune system has long been recognized and immunomodulation induced by anaesthesia may be implicated in the dissemination of tumour metastasis and the incidence of postoperative infection. Of the many studies of the effects of anaesthesia on the immune system, some give conflicting results. The reasons for this are unclear, but difficulties exist in quantifying the role of anaesthesia in postoperative immune dysfunction.

Surgical trauma is known to cause a general loss of immune responsiveness or anergy, making it difficult to separate the contribution of the anaesthetic agents to postoperative immunosuppression (Stevenson et al, 1990). Anaesthesia also modifies the endocrine stress response to surgery, thereby subtly altering the complex interaction between the neuroendocrine and immune systems. Etomidate, for instance, inhibits adrenal steroidogenesis and its prolonged use for sedation in the intensive care environment has been associated with increased mortality secondary to hypocortisolaemia (Watt and Ledingham, 1984).

In addition, many tests of immunocompetence involve the sampling of peripheral blood, which may be a poor indicator of events occurring in the lymphoid tissues. These problems have led many to conduct in-vitro research where conditions can be more tightly controlled and regulated. Unfortunately in-vitro experiments may not give an accurate reflection of events happening at tissue level, since it is unlikely that the activation of cells is not altered when they are removed from the body. Studying specific cell types in isolation may also be a poor indicator of immune competence.

Nevertheless, a large number of in-vitro and in-vivo experiments demonstrate a short-lived and reversible depression of immune function by anaesthetic agents (*Table 1*). Before examining this in greater detail it is worth briefly considering the basic structure of the immune system.

OVERVIEW OF THE IMMUNE SYSTEM

The immune system (*Figure 1*) is necessarily complex because of the myriad of organisms and foreign antigens that can invade and damage the body. It has three cardinal features: specificity, self-discrimination and memory. Immunity can be either innate or specific (*Table 2*).

Innate immunity provides the first line of defence, requires no previous exposure to the invading organism and therefore has the advantage of speed. The main components are phagocytes (macrophages, neutrophils), complement and acute phase reactants such as C-reactive protein. Specific immunity requires previous exposure for an optimal response. Subsequent encounters provoke a greatly increased defence mechanism. The specific immune response also directs components of the immune response towards the site of antigen entry, greatly increasing the effectiveness of elimination of the organism. The lymphocyte is the

Dr John D Hunter is Specialist Registrar in the Department of Anaesthetics and Intensive Care, Aberdeen Royal Infirmary, Aberdeen AB25 2ZN

TABLE 1.
Effects of anaesthesia and surgery on the human immune system

Immunomodulatory effect				Anaesthetic drugs and techniques	Reference
T lymphocyte function	Lymphocyte proliferation	In-vivo studies suggest a decrease in T cell responsiveness		Combination of general anaesthesia + surgery	Hole (1984), Stevenson et al (1990)
		In-vitro studies yield conflicting results	No demonstrable effect	Intravenous induction agents	Devlin et al (1994)
			Decreased T cell response	Nitrous oxide, halothane	Bruce (1976), Stevenson et al (1990)
	NK cell cytotoxicity	In-vivo studies suggest a decrease in NK cytotoxicity		Exposure to nitrous oxide, enflurane and halothane	Woods and Griffiths (1986)
		In-vitro studies also suggest a decrease in cytotoxicity		Combination of general anaesthesia + surgery	Tonnesen and Wahlgreen (1988)
				Opioid analgesics	Beilin et al (1996), Yeager et al (1995)
Antigen processing	Downregulation of MHC class II expression on lymphocytes and monocytes			High dose fentanyl anaesthesia	McBride et al (1994)
Cytokines	Decreased IL-6 release			Alfentanil	Crozier et al (1994)
	Increased TNF-α from monocytes			Thiopentone, propofol and ketamine	Rossano et al (1992)
Neutrophil function	Neutrophil polarization inhibited			Propofol, thiopentone	O'Donnell et al (1992)
	Respiratory burst inhibited			Propofol, midazolam, ketamine and methohexitone	Heine et al (1996)
	Neutrophil chemotaxis inhibited			Halothane, enflurane, and propofol	Moudgil and Forrest (1984), Jensen et al (1993)

IL = interleukin; MHC = major histocompatability complex; NK = natural killer; TNF = tumour necrosis factor

principal immunocompetent cell, and is responsible for the specificity of the immune response. Three types of lymphocyte exist: B lymphocytes, T lymphocytes and natural killer (NK) cells.

T lymphocytes

T lymphocytes are so called because they are matured by the thymus. There are two major subsets of T cells: helper T cells (T_H) and cytotoxic T cells (T_C). Most T_H cells express a surface glycoprotein called $CD4^+$, while most T_C cells express $CD8^+$. T lymphocytes have an antigen binding molecule or T cell receptor (TCR) on their surface. TCRs can only react with antigens bound to the human leucocyte antigen (HLA), a specialized cell surface glycoprotein encoded by genes of the major histocompatibility complex (MHC).

Antigen-presenting cells (APCs) such as the macrophage process foreign antigens so that small peptides belonging to the antigen are bound to the MHC molecule and are recognized by the T cells. Two main forms of MHC exist: class I and class II. Class I molecules are present on the surface of almost all nucleated cells, while class II molecules are mainly confined to APCs and B cells. CD4+ T lymphocytes recognize antigens in association with MHC class II and CD8+ T_C cells recognize antigens in association with class I gene products.

T_C cells lyse target cells, e.g. virally infected cells, whereas T_H cells initiate specific immunity. Cytokines play an integral role in this process.

NK cells are a subset of lymphocytes that appear as large lymphocytes with numerous cytoplasmic granules and are sometimes called large granular lymphocytes. They do not express TCR and MHC molecules do not restrict activation. NK cells are capable of killing certain tumour cells or virally infected cells.

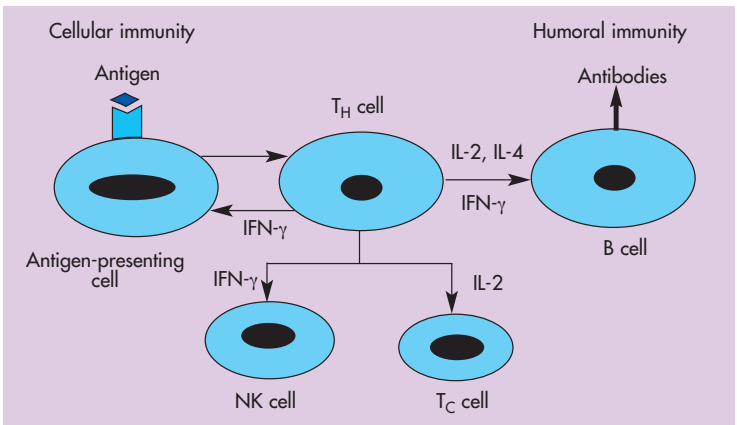

Figure 1. Activation of the immune system. Antigen is presented to the T helper (T_H) cells by antigen-presenting cells. The T_H cells then secrete cytokines which activate cytotoxic T cells (T_C) and natural killer (NK) cells. B cell activation leads to the secretion of antibodies. IFN-γ = interferon-γ, IL = interleukin.

TABLE 2.
Components of the immune system

Component	Innate	Specific
Humoral	Complement, C-reactive protein	Antibodies
Cellular	Macrophages, neutrophils, natural killer cells	Lymphocytes
Cytokines	Macrophage-derived cytokines, e.g.tumour necrosis factor-α	Lymphocyte-derived cytokines, e.g. interferon

There is considerable interaction between the two components of the immune system

B lymphocytes

B lymphocytes differentiate in the bone marrow. These mature into plasma cells which can produce antibodies to neutralize and eliminate the antigen that induced their formation. B lymphocyte activation is facilitated by T_H cells and requires an antigen to bind to the membrane immunoglobulin (Ig) on the B cell. Activated B cells enlarge and many mature into Ig-secreting plasma cells, while others form memory cells that survive without further antigenic stimulation, but generate a rapid response on re-exposure to the antigen.

Cytokines

Cytokines are low molecular weight proteins produced by multiple diverse cell types during the effector phase of specific and innate immunity. Individual cytokines often act on many different cells, by binding to cell surface receptors, which stimulates production of mRNA and thus protein synthesis. They play a pivotal role in the regulation of immune and inflammatory responses.

The complement system

The complement system consists of serum and membrane proteins that interact in a cascade-like manner to produce active protein products that enhance phagocytosis of organisms, and mediate membrane lysis and inflammation. Two pathways of activation exist, the classical and alternative pathways, which converge in the activation of C3. This leads to the formation of a cytolytic protein complex known as the membrane attack complex. The classical pathway is triggered by antigen–antibody complexes, while the alternative pathway is initiated by the surfaces of certain organisms, e.g. endotoxin or yeast cell walls. The complement system is usually tightly regulated to prevent widespread release of inflammatory mediators.

Phagocytes

Macrophages are released into the circulation as monocytes and mature in tissues such as the spleen and lymph nodes. They are phagocytic and effective at presenting antigens to T cells. They have surface receptors that recognize the Fc region of antibodies as well as biologically active fragments of complement (C3b). They produce a wide variety of cytokines.

Neutrophils are stored in the bone marrow and are rapidly released into the circulation in response to foreign antigens. Neutrophils also possess receptors for the Fc portion of antibodies and they migrate to and accumulate at sites of complement activation. Their primary function is elimination and degradation of bacteria, which often involves the generation of oxygen-derived free radicals.

EFFECTS OF ANAESTHESIA

T lymphocyte function

The combination of anaesthesia and major surgery causes lymphopenia. This reduction in lymphocyte count is probably mediated by the endocrine stress response, and occurs because lymphocytes are redistributed from peripheral blood into lymphatic tissue (Toft et al, 1993). T lymphocyte numbers return to preoperative values within days.

A substantial number of studies investigating T cell function are based on experiments in which T cells are activated in a controlled manner and their proliferation quantified by the incorporation of a radioactively labelled precursor into the newly synthesized DNA. Commonly used T cell activating mitogens include concanavalin A (ConA) and phytohaemagglutinin (PHA).

The majority of in-vivo studies suggest that there is a decrease in lymphocyte proliferation in response to mitogens after surgery and anaesthesia, the extent of the depression increasing with the extent of surgical trauma (Hole, 1984). However, a study by Duncan et al (1976), in which volunteers were exposed to prolonged halothane or enflurane anaesthesia with no surgical insult, failed to show any significant alteration in the ability of the subjects' lymphocytes to transform in response to PHA compared with pre-anaesthetic values or unanaesthetized controls.

Devlin et al (1995) examined the effects of propofol and thiopentone on delayed type hypersensitivity (DTH) reactions and T lymphocyte proliferation in healthy volunteers. This is of interest since DTH responses test not only the ability of the immune system to recognize foreign antigens, but also its effectiveness in dealing with them. They demonstrated that both drugs caused no depression of PHA-induced T cell proliferation, but caused significant depression of DTH reactions to skin multi-test antigens. This may be of clinical importance since a reduced DTH response is associated with increased mortality in surgical patients (Christou et al, 1995).

In-vitro studies examining the effects of inhalational and intravenous anaesthetic agents on T cell proliferative responses to mitogens have found conflicting results, with several failing to show any decrease in T cell response after exposure to these agents (Bruce, 1976; Devlin et al, 1994).

Anaesthesia and surgery also affect NK cytotoxicity. Woods and Griffiths (1986) showed that NK cell activity was transiently depressed after in-vitro exposure to clinical concentrations of general anaesthetics nitrous oxide, halothane and enflurane, but returned to normal 1 hour after withdrawal of anaesthetic. When anaesthesia and surgery are combined, there is a rapid and transient

increase in NK cell activity in blood drawn intraoperatively, followed by a postoperative decline in activity (Tonnesen and Wahlgreen, 1988). This transient increase may be caused by NK cell mobilization from lymphoid tissue into the circulation.

Intra- and postoperatively administered opiates may be implicated in the suppression of immune function. Beilin et al (1996) compared NK cytotoxicity in patients receiving high doses (75–100 μg/kg) and low doses (up to 5μg/kg) of fentanyl as part of their anaesthetic regimen. In both groups there was a similar suppression of NK cell activity. However, patients receiving the high doses of fentanyl still had significantly impaired NK cell cytotoxic activity at 48 hours, whereas in the low dose fentanyl group the NK cell cytotoxic activity had returned to normal.

Yeager et al (1995) examined the effects of morphine on NK cell natural cytotoxicity in healthy volunteers. They demonstrated significant suppression of NK cell natural cytotoxicity 2 and 24 hours after the onset of intravenous morphine exposure, which persisted for 24 hours after termination of the morphine in those receiving higher doses. The mechanisms by which opioids suppress NK cell natural cytotoxicity are not clear, but are probably multifactorial and centrally mediated.

Antigen processing

As discussed T_H and T_C cells only recognize and respond to foreign antigens when a portion of the antigen is presented in association with MHC antigens. MHC class II antigens are critical to the T cell response, because T_H cells will only recognize and respond to foreign antigens presented on the macrophage/monocyte cell surface. A direct relationship has been established between the ability of monocytes to express MHC class II antigens and subsequent development of postoperative infections. McBride et al (1994) showed that high dose fentanyl induction for cardiac surgery was rapidly followed by downregulation of MHC class II expression on lymphocytes and monocytes.

B lymphocytes

Data regarding the effects of anaesthesia on B lymphocyte activation are scarce. Stevenson et al (1990) exposed B lymphocytes to halothane in-vitro and measured the proliferative capacity of the lymphocyte to mitogen stimulation, but showed no significant difference in proliferation from controls. In another study pokeweed mitogen-stimulated lymphocytes from humans were incubated with clinically relevant concentrations of thiopentone (Salo, 1989). B lymphocyte function was assessed by measuring IgG, IgM and IgA production. No inhibition of Ig production was seen after 1 hour of exposure of the lymphocytes to induction concentrations of thiopentone.

Most B cell effects seem to be mediated by a combination of anaesthesia and surgery. A decline in B lymphocyte numbers is seen postoperatively but this is probably caused by haemodilution rather than an effect on Ig synthesis, since the half-life of serum Ig is measured in days. A postoperative decrease in the proliferative response to mitogens has been reported. Eskola et al (1984) reported that pokeweed mitogen-induced B lymphocyte transformation was depressed at the end of the operative procedure, but there was no reduction in pokeweed mitogen-induced transformation during anaesthesia before surgery. In addition, it took 6–7 days after the operation for values to return to those recorded before anaesthesia.

Complement

The combination of surgery and anaesthesia is associated with controlled activation of the complement system but there are no data on the in-vitro effects of anaesthetics on the activity of complement compounds. However, the complement system is involved in a large number of adverse reactions that occasionally occur in response to intravenous anaesthetic agents. Direct 'alternative pathway' activation of complement by drugs administered for the first time is possible.

Monocytes/macrophages

Monocytes play a crucial role in the non-specific immune response. The combination of anaesthesia and surgery is known to decrease the cytolytic and phagocytic capabilities of monocytes. Inhibition of monocyte chemotaxis is seen when separated monocytes are exposed to clinical concentrations of a variety of local, intravenous and volatile anaesthetic drugs. This inhibition is reversible and may be caused by the drugs acting directly on the mechanisms of locomotion. In-vitro studies of thiopentone on monocytes show that thiopentone decreases cytolysis of tumour cells when monocytes are stimulated by mitogens (Hole, 1984).

Neutrophils

Polymorphonuclear leucocytes or neutrophils have a pivotal role in the immunological response to invading bacteria. This is reflected in the large number of studies examining the effects of anaesthesia on neutrophil function and the relative ease by which the cell functioning can be assessed.

Nakagawara et al (1986) reported that three commonly used inhalational agents, halothane, enflurane and isoflurane, reversibly inhibited production of superoxide ions (O_2^-) by neutrophils in-vitro. They suggested that inhibition of O_2^-

production may be caused by defective movement of calcium ions in volatile anaesthetic-treated neutrophils, since volatile anaesthetic agents may inactivate proteins involved in calcium ion transport across neutrophil membranes.

An in-vitro study by Heine et al (1996) utilizing flow cytometry demonstrated that propofol, midazolam, ketamine and methohexitone all showed similar inhibition of respiratory burst (1–6%) at sedating concentrations, but at anaesthetic and 10-fold anaesthetic concentrations, propofol had significantly greater inhibitory properties. It was suggested that its lipid carrier (10% Intralipid) may have been responsible since it caused similar inhibition of respiratory burst by neutrophils.

O'Donnell et al (1992) reported the effects of propofol, thiopentone and midazolam on neutrophil polarization in-vitro. Polarization is the initial response to a chemotactic stimulus and involves the neutrophil changing shape. At clinically relevant concentrations, midazolam did not affect polarization while propofol and thiopentone produced approximately 59% inhibition, which became complete with higher drug concentrations.

Others have studied the effects of anaesthetic agents on chemotactic locomotion of neutrophils. Halothane and enflurane were shown to depress chemotactic migration in-vitro at 1 minimum alveolar concentration (MAC), while isoflurane failed to affect neutrophil migration (Moudgil and Forrest, 1984). Propofol adversely affects the random and chemotactic locomotion of human polymorphonuclear leucocytes (Jensen et al, 1993).

Cytokines

Cytokines have only been precisely identified relatively recently and as such little work exists on the effects of anaesthesia on cytokine production.

An in-vitro study by Crozier et al (1994) suggests that the type of anaesthesia may influence cytokine release. They measured interleukin-6 (IL-6) concentration, which is known to increase after surgical trauma, in two groups of patients undergoing hysterectomy. One group received inhalational anaesthesia with isoflurane and nitrous oxide while the other received total intravenous anaesthesia with alfentanil and propofol. Those receiving total intravenous anaesthesia had a lower IL-6 response. It was postulated that alfentanil was responsible for the attenuated response because monocytes are known to have opioid receptors. Opioid binding to these receptors reduces concentrations of intracellular cyclic adenosine monophosphate (c-AMP), a second messenger necessary for the release of IL-6. IL-6 levels have been shown to be a sensitive predictor of outcome in those with severe intra-abdominal sepsis.

An in-vivo study reported that intravenous induction agents could increase production of cytokines from human monocytes (Rossano et al, 1992). Thiopentone, propofol and ketamine all caused a 4–5-fold increase from controls in TNF-α production from monocytes. Propofol induced the greatest increase in IL-1 production, while IL-6 release was notably increased by ketamine. Isoflurane inhibits the secretion of TNF-α and IL-1 from stimulated lymphocytes. The mechanism underlying the modification of cytokine secretion by anaesthetic agents is unknown.

REGIONAL ANAESTHESIA AND THE IMMUNE RESPONSE

There is evidence that regional anaesthesia may lessen the immunosuppressive changes seen postoperatively, by attenuating the endocrine stress response to surgery. Hashimoto et al (1995) showed that extradural anaesthesia prevents changes in lymphocyte subpopulations in gastrectomy patients. There was a decrease in CD4+ and an increase in CD8+ lymphocytes measured after skin incision in those receiving general anaesthetic, which was not observed in patients receiving epidural anaesthesia. The authors suggested that extradural anaesthesia may be immunologically beneficial during the postoperative period.

NK cell cytotoxicity may also be altered by extradural anaesthesia (Tonnesen and Wahlgreen, 1988). Postoperative NK activity was measured in two groups of patients undergoing abdominal hysterectomy: one group received extradural anaesthesia, and the other neuroleptanaesthesia. In the latter group NK activity was impaired for 3 days after the operation while no significant suppression of NK function was seen in the extradural group. The reason for this is unknown but may be related to an alteration in the stress response to surgery induced by extradural anaesthesia.

Neutrophil chemotaxis and bacteriocidal activity was greater in those patients who had arthroplasty performed under spinal anaesthesia compared with general anaesthesia (Erskine et al, 1994).

It has been reported that extradural anaesthesia can have a beneficial effect on monocyte function. Monocyte-mediated lysis of tumour target cells was measured in patients undergoing hip arthroplasty under either general or extradural anaesthesia. The cytolytic capacity of the lymphocytes from patients receiving regional anaesthesia was virtually unchanged from preoperative values, while monocytes from the general anaesthesia group showed a significantly reduced ability to lyse tumour cells (Hole et al, 1982).

Few studies have examined the effects of regional anaesthesia on cytokine production, but

Moore et al (1994) found extradural analgesia did not alter circulating IL-6 levels after pelvic surgery.

CONCLUSIONS

It is difficult to quantify the effect that anaesthesia has on the immune system because numerous confounding factors are involved. Available evidence does seem to suggest that anaesthetic agents have a short-term but reversible effect on host defence mechanisms. The causes of this are still unclear, and will only be unravelled with a much greater understanding of the immune response and the mechanisms by which anaesthetics exert their effects at a cellular level.

To date, there is no direct evidence to suggest that any one anaesthetic or anaesthetic technique is associated with a higher post-surgical infection rate, or increased incidence of tumour metastasis. The immunosuppressive properties of anaesthetic agents appear to be short-lived, and may be more pertinent in the intensive care environment where they are used for prolonged periods to sedate critically ill patients. An in-vitro study demonstrated that propofol reduced proliferative responses of lymphocytes from intensive care patients but had no effect on lymphocytes from healthy volunteers (Pirttikangas et al, 1993). This suggests that intensive care patients, who already have immune dysfunction, may be more vulnerable to immunomodulation by anaesthetics. There has also been a reported association between the development of pneumonia in ventilated head injury patients and the use of thiopentone for sedation, but this was only an incidental finding of the study (Braun et al, 1986).

Our understanding of the way in which anaesthesia interacts with host defence mechanisms is still at a rudimentary stage and until further research is performed on this complex subject the contribution of anaesthesia to postoperative immune dysfunction will remain unclear. HM

Beilin B, Shavit Y, Hart J (1996) Effects of anaesthesia based on large *vs* small doses of fentanyl on natural killer cell cytotoxicity in the perioperative period. *Anesth Analg* **82:** 492–7

Braun SR, Levin AB, Clark KL (1986) Role of corticosteroids in the development of pneumonia in mechanically ventilated head-trauma victims. *Crit Care Med* **14:** 198–201

Bruce DI (1976) Failure of nitrous oxide to inhibit transformation of lymphocytes by phytohemagluttinin. *Anesthesiology* **44:** 155–6

Christou NV, Meakins JL, Gordon J (1995) The delayed hypersensitivity response and host resistance in surgical patients. *Ann Surg* **222:** 534–48

Crozier TA, Muller JE, Quittkat D et al (1994) Effect of anaesthesia on the cytokine responses to abdominal surgery. *Br J Anaesth* **72:** 280–5

Devlin EG, Clark RSJ, Mirakhur RK (1994) Effect of four i.v. induction agents on T-lymphocyte proliferation to PHA in vitro. *Br J Anaesth* **73:** 315–17

Devlin EG, Clark RSJ, Mirakhur RK (1995) The effects of thiopentone and propofol on delayed hypersensitivity reactions. *Anaesthesia* **50:** 496–8

Duncan PG, Cullen BF, Calverly R (1976) Failure of enflurane and halothane anesthesia to inhibit lymphocyte transformation in volunteers. *Anesthesiology* **46(6):** 661–5

Erskine R, Janicki PK, Neil G et al (1994) Spinal anaesthesia but not general anaesthesia enhances neutrophil biocidal activity in hip arthroplasty patients. *Can J Anaesth* **41:** 632–8

Eskola J, Salo M, Viljanen MK (1984) Impaired B lymphocyte function during open-heart surgery. *Br J Anaesth* **56:** 333–7

Hashimoto T, Hashimoto S, Hori Y (1995) Epidural anaesthesia blocks changes in peripheral lymphocytes subpopulation during gastrectomy for stomach cancer. *Acta Anaesthesiol Scand* **39:** 294–8

Heine J, Leuwer M, Scheinichen D (1996) Flow cytometry evaluation of the in-vitro influence of four i.v. anaesthetics on respiratory burst of neutrophils. *Br J Anaesth* **77:** 387–92

Hole A (1984) Depression of monocytes and lymphocytes by stress related humoral factors and anaesthetic related drugs. *Acta Anaesthesiol Scand* **28:** 280–6

Hole A, Unsgaard G, Breivik H (1982) Monocyte functions are depressed during and after surgery under general anaesthesia but not under epidural anaesthesia. *Acta Anaesthesiol Scand* **26:** 301–7

Jensen AG, Dahlgren C, Eintrei C (1993) Propofol decreases random and chemotactic stimulated locomotion of human neutrophils in vitro. *Br J Anaesth* **70:** 99–100

McBride WT, Armstrong MA, Crockard AD et al (1994) Selective reduction in leucocyte antigen expression after high-dose fentanyl administration at cardiac surgery. *Br J Anaesth* **73:** 717P–718

Moore CM, Desborough JP, Powell H (1994) Effects of extradural anaesthesia on interleukin-6 and acute phase response to surgery. *Br J Anaesth* **72:** 272–9

Moudgil GC, Forrest JB (1984) Comparative effects of volatile anaesthetic agents and nitrous oxide on human leucocyte chemotaxis in vitro. *Can Anaesth Soc J* **31(6):** 631–7

Nakagawara M, Takeshigne K, Takamatsu J et al (1986) Inhibition of superoxide production and Ca2+ mobilisation in human neutrophils by halothane, enflurane and isoflurane. *Anesthesiology* **64:** 4–12

O'Donnell NG, McSharry CP, Wilkinson PC et al (1992) Comparison of the inhibitory effect of propofol, thiopentone and midazolam on neutrophil polarisation in vitro in the presence or absence of human serum albumin. *Br J Anaesth* **69:** 70–4

Pirttikangas CO, Pertilla J, Salo M (1993) Propofol emulsion reduces proliferative responses of lymphocytes from intensive care patients. *Intens Care Med* **19:** 299–302

Rossano F, Tufano R, Cipollaro De LàErgo et al (1992) Anaesthetic agents induce human mononuclear leucocytes to release cytokines. *Immunopharmacol Immunotoxicol* **14:** 439–50

Salo M (1989) Effects of thiopentone on immunoglobulin production in vitro. *Br J Anaesth* **63:** 716–20

Stevenson GW, Hall SC, Rudnick S et al (1990) The effect of anaesthetic agents on the human immune response. *Anesthesiology* **72:** 542–52

Toft P, Svendsen P, Tonnesen E (1993) Redistribution of lymphocytes after major surgical stress. *Acta Anaesthesiol Scand* **37:** 245–9

Tonnesen E, Wahlgreen C (1988) Influence of extradural and general anaesthesia on natural killer cell activity and lymphocyte subpopulations in patients undergoing hysterectomy. *Br J Anaesth* **60:** 500–7

Watt I, Ledingham IMcA (1984) Mortality amongst multiple trauma patients admitted to an intensive therapy unit. *Anesthesia* **39:** 973–81

Woods GM, Griffiths DM (1986) Reversible inhibition of natural killer cell activity by volatile anaesthetic agents in vitro. *Br J Anaesth* **58:** 535–9

Yeager MP, Colacchio T, Yu CT (1995) Morphine inhibits spontaneous and cytokine enhanced natural killer cell cytotoxicity in volunteers. *Anesthesiology* **83:** 500–8

KEY POINTS

- The available evidence suggests that anaesthetic agents exert a short-term depression of immune responsiveness.
- It is unknown whether this immunomodulation influences perioperative infection rates or aids in the dissemination of tumour metastasis.
- Prolonged infusion of anaesthetic agents for sedation in the critically ill may exacerbate the immunosuppression that already exists in these patients.
- Regional anaesthesia appears to attenuate some of the deleterious effects of anaesthesia on the immune system.