While the cross-talk between the nervous and immune systems is slowly being unravelled, important commonalities between the two systems suggest that anaesthetics may impact profoundly on the immunity, similar to the nervous system. For example, many immune cells are ‘excitable cells’, have plasma membranes that depolarize (e.g. the macrophage membrane after phagocytosis), and express neurotransmitter receptors like neurones. Immune cells express γ-aminobutyric type A (GABA$_A$) receptors, an anaesthetic target for benzodiazepines, propofol and the volatile anaesthetics. An important target of ketamine, nitrous oxide, xenon, the $N$-methyl-$d$-aspartate (NMDA) receptor may also be expressed. Expression of these receptors may explain accumulating data suggesting that many anaesthetic drugs exert important functional effects on immune cells (although the reader is recommended to read the article on opioids by Al-Hashimi and colleagues reviewing evidence for immune cell opioid receptor expression). The diffuse nature of receptor expression of neurotransmitter receptors mean that anaesthetic effects on immunity may include altered innate and acquired inflammatory responses. It is possible that the functional consequences of these effects may include increased vulnerability to infection and cancer. However, reducing intraoperative inflammation may be a
cruical benefit of anaesthesia contributing to preserve perioperative organ function.\textsuperscript{2,13} It is also unclear whether the ‘hangover’ after an anaesthetic includes prolonged changes in immune function as can occur in other organ systems.\textsuperscript{14,15}

In this issue of the British Journal of Anaesthesia, Fahlenkamp and colleagues\textsuperscript{16} explore the immune effects of two different anaesthetic drugs, sevoflurane and xenon, on leucocyte function. The rationale for this study stemmed from preclinical observations suggesting that xenon, in contrast to other anaesthetics, may induce proinflammatory cytokine release. The authors tested the hypothesis that xenon and sevoflurane would exert differing effects on inflammation in a randomized controlled trial of patients undergoing elective abdominal surgery. Several interesting observations are made in this pragmatic, but small, trial. During anaesthesia, the total number of circulating leucocytes (especially lymphocytes and granulocytes) decreased in the sevoflurane group in the first hour but was not altered in the xenon group. The authors postulate that this occurred secondary to haemodilution in the sevoflurane group as increased fluids were administered for haemodynamic support. An alternative explanation may be that circulating cytokine and chemokine levels were different between the two groups, leading to reduced immune cell mobilization under sevoflurane anaesthesia. Unfortunately, circulating chemokine and cytokine levels were not measured. Rather the authors conducted ex vivo functional analysis of cells by stimulating cytokine release from circulating cells captured by venous sampling. These studies are of interest as they test the possibility of an anaesthetic ‘hangover’ on immunity as the gases will wash out early during the 4 h test period. The possibility that anaesthetics exert prolonged effects on both cells and organ systems has been recognized for sometime and is increasingly being investigated under the term ‘preconditioning’.\textsuperscript{14,15} Essentially in Fahlenkamp and colleagues’ study, the authors tested whether either anaesthetic exerted a more prolonged effect on immune cell function. However, the authors found no difference between the gases. While this does not prove, there is no immune ‘hangover’ (this would require a group that does not receive anaesthesia); clinically, these two very different anaesthetic drugs were inseparable. This may reflect recent data suggesting immune cells express both GABA\textsubscript{A} and NMDA receptors, and that both these receptors play a role in modulating the immune response. However, definitive conclusions are hampered by the presence of other drugs, such as midazolam that has a longer half-life, and so may have exerted a more prolonged effect on the immune responses.\textsuperscript{5,9} Another consideration is that the immune effects of the ongoing surgery outweighed any differences in the effects of anaesthetic drugs themselves. Essentially, the immune response to the trauma of surgery may have greater impact than any small differences in the anaesthetic’s immune profile.

Nonetheless, despite very different neural mechanisms of action of sevoflurane and xenon, the drugs share quite a similar immune profile. An extrapolation may be that we expect little difference clinically between the two agents on immune consequences such as infection. Unfortunately, the study sample size was too small to meaningfully include functional outcomes, such as infection, as a secondary outcome parameter. In the future, we must perform large enough studies to focus on these clinically important endpoints. This is emphasized by data suggesting that avoidance of benzodiazepine sedation in septic patients may reduce mortality from sepsis,\textsuperscript{9} or secondary infections in the intensive care unit.\textsuperscript{10} Similarly, benzodiazepines have been associated with increased mortality from pneumonia in patients.\textsuperscript{9} Supporting preclinical data suggest that this may involve targeting of immune cell GABA\textsubscript{A} receptors, leading to intracellular acidosis, but further data are needed.\textsuperscript{5} Whether the single dose of midazolam administered in Fahlenkamp and colleagues’ study exerts significant effects on immune outcomes is unknown.

The association of regional anaesthesia with reduced cancer recurrence is another example of the need to focus on clinically relevant immune endpoints. Here reduced opioid consumption, and therefore reduced immune sequelae of opioid drugs, is suggested to reduce the risk of cancer recurrence.\textsuperscript{11} These data largely derive from retrospective observational studies and recent meta-analysis did not support the association.\textsuperscript{11} Prospective studies, including randomized controlled trials, are still awaited to address the issue of cancer recurrence. Nonetheless, meta-analysis has again suggested that regional anaesthesia conferred an overall survival benefit for colorectal surgery\textsuperscript{11} with a more recent study suggested mortality benefit from joint replacement surgery.\textsuperscript{11} Regional anaesthesia can modulate the intertwined inflammatory (when combined with an \textalpha 2 adrenergic agonist),\textsuperscript{18} sympathetic and neurohumoral responses;\textsuperscript{19} mechanistic studies are still required to further probe the connection between regional anaesthesia and improved long-term outcomes.

Another example is the use of steroids to modulate perioperative inflammation to reduce the risk of postoperative atrial fibrillation and possibly reduce length of hospital and ICU stay.\textsuperscript{25} However, the results of two, ongoing, large, randomized controlled trials, focusing on mortality and other morbidity such as myocardial infarction, are eagerly awaited to define the role of steroids in cardiac anaesthesia.

Attention to intraoperative temperature control, to reduce the burden of infection, may have been the first step in actively modifying the perioperative immune response. At present, there is a lack of data to argue for further specific modifications of current practice. The avoidance of longer acting drugs with neural and immune cells consequences, such as midazolam, or the wider adoption of specific regional anaesthetic techniques and drugs, may be the next step. However, such proposals need testing in randomized controlled trials that focus on functional benefits such as infection.

Declaration of interest

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