# "Killing Me Softly?"
# *The long-term effects of anaesthesia*

***Zuccherelli L***
Dunkeld Anaesthetic Practice, Johannesburg

**Correspondence to**: Dr Lisa Zuccherelli, e-mail: lisazucc@iafrica.com

***SAJAA 2007; 13(6): 5-10***

## Introduction

Historically, anaesthetists have believed that their actions only have immediate or short-term consequences. Morbidity or mortality that occurs after discharge is invariably assumed to be secondary to the patient's underlying medical condition. Recently, a growing body of evidence has emerged suggesting that anaesthesia may have long-term implications in susceptible individuals, particularly in patients anaesthetised at the extremes of age. Research suggests that anaesthetic agents may be neurotoxic under certain circumstances, and this has raised the possibility that even a routine anaesthetic might pose a risk to the vulnerable brains of the very young and the elderly.

Scientific data is extremely sparse at present, and there are many limitations to the evidence that currently exists. In particular, most of the research has been carried out either in vitro or in animal models, and there is deserved scepticism concerning the extrapolation of animal data to humans. Nevertheless, enough concern has been generated in the relevant medical circles to warrant the Anaesthesia Patient Safety Foundation (APSF) of America convening an experts' workshop in September 2004 to discuss long-term outcomes after surgery and anaesthesia (8). Considering that mortality rates in the first year after surgery are as high as 5 – 14% in certain patient populations, small improvements in these rates could save many lives each year.

Inflammation has been implicated in many disease processes and is one of the factors that may impact on long-term outcomes after surgery. Anaesthetic agents can directly and indirectly alter the function of the immune system, and may have subtle, but important effects on morbidity and mortality. Available evidence suggests that the anti-inflammatory and immunosuppressive effects of anaesthesia can affect the progression and acuity of certain chronic illnesses. It can also increase the frequency of disease-related complications and death.

Finally, with renewed interest in the long-term effects of anaesthesia, comes the inevitable concern regarding the possible adverse effects of occupational exposure to anaesthetic agents. Despite improvements in scavenging systems and operating room ventilation, contamination of the working environment remains unavoidable whenever inhalational agents are used to induce and/or maintain anaesthesia. A number of medical complaints have been reported in theatre staff, ranging from trivial to serious, and there is ongoing concern that these may somehow be related to occupational exposure.

This editorial will review the latest research on the long-term effects of anaesthesia, particularly in patients at the extremes of age. It will also examine some of the pathophysiological mechanisms that have been implicated. The role of inflammation and the effects of anaesthesia on the immune system will be discussed, as well as the long-term risk (if any) of occupational exposure to anaesthetic agents.

## Long-term effects of anaesthesia in the very young

### *Developmental susceptibility to neurodegeneration*

Neuronal apoptosis, or programmed cell death, takes place during normal development of the central nervous system (CNS). Apoptosis is a physiological process initiated by the nuclei of normally functioning cells, and it is a process in which neurons are programmed to commit suicide if their synaptic mission is thwarted to some critical degree. Disruption or exacerbation of apoptosis by genetically determined disturbances, environmental factors, drugs and stressors (e.g. pain, hypoglycaemia, hypoxia and ischaemia) may result in neurodevelopmental disorders in the foetus.

Recently, studies in animal models have shown that transient interference in the action of certain neurotransmitters during a critical stage of development can trigger apoptosis of millions of neurons that otherwise would not have been deleted from the developing brain. This stage of development is known as synaptogenesis, and in the human brain, correlates with a period of rapid growth (brain growth spurt). In humans, the normal brain growth spurt starts in the sixth month of pregnancy and extends to the third year after birth.

In the immature mammalian brain, neuronal apoptosis can be triggered by the transient blockade of glutamate N-methyl-d-aspartate (NMDA) receptors, or the excessive activation of -aminobutyric acid (GABA) receptors. Since the commonly used anaesthetic agents have strong affinity for these receptors, it has been postulated that anaesthetic agents may induce apoptosis of immature neurons via the same receptor-mediated processes seen in animal models. Ketamine and nitrous oxide are potent NMDA-receptor antagonists, whilst propofol, volatile agents, benzodiazepines and barbiturates are GABA- agonists. The brain develops under the influence of neural input as the foetus interacts with its environment, whereas anaesthesia removes the input and suppresses normal neural traffic, and may consequently decrease synaptogenesis.

Ethanol provides a prime example of an agent that, by interfering with neurotransmitter systems, can delete large numbers of neurons and give rise to neurobehavioural disturbances and physical abnormalities collectively known as foetal alcohol syndrome (FAS). Ethanol is a potent NMDA- antagonist and GABA-agonist, and studies in rodents show that administration of ethanol to infant rats triggers robust neuroapoptosis. In addition, superimposing the neurodegeneration pattern that results from treating infant rats with NMDA-antagonists and GABA-agonists results in the same degeneration pattern caused by ethanol. Especially noteworthy is the fact that it only requires a single intoxication episode for foetal brain damage to occur in the rat model.

### *Studies using rodents*

A number of animal studies have been conducted that evaluate

the effects of NMDA-antagonists and GABA-agonists on the developing brain. Much of the work has focussed on ketamine, which does not imply that the risk of neurodegeneration is greater with ketamine. Rather, it is simply the drug with the most preclinical data.

The first reported study to indicate that NMDA-receptor antagonists could produce neurotoxicity was published in 1999 by Ikonamidou et al. Studies in rats demonstrated that MK-801 (an NMDA-antagonist) and ketamine led to widespread apoptotic neuro-degeneration in the developing rat brain. This study also indicated an age-related sensitivity correlating with the period of synaptogenesis in humans, with no apoptosis occurring in the infant rat brains exposed to these agents after postnatal day 21.

The concerns raised in this study about the safety of ketamine in infants and young children warranted further investigation to confirm and elaborate on the original findings. Scallet et al confirmed histologically that the ketamine dosing regimen used in the original study did result in apoptosis in rat pups, but less aggressive dosing did not, suggesting that the neurotoxicity of ketamine depends on the dose administered and the duration of exposure.

Following these preliminary studies, it became important to attempt to extrapolate these findings to humans in order to determine whether or not this is a clinical problem at currently administered doses of anaesthetic agents, and which age groups are most at risk. The period of synaptogenesis during which rodents are most vulnerable, corresponds to human development that occurs approximately from the third trimester *in utero* through the third year of life. In addition, there is a second period of accelerated synaptogenesis that occurs during adolescence, and there is some evidence that there is increased neurological vulnerability to the effects of alcohol and certain drugs used recreationally during this time.

Based on the evidence in rodents, the scientific community recommended non-human primate studies should be carried out as soon as possible. Primate studies have been commenced, but for logistical reasons, they have been outpaced by the rodent data being generated internationally. Jevtovic-Todorovic et al reported apoptosis in neonatal rats exposed to 6 hours of "mock anaesthesia" using isoflurane, nitrous oxide and midazolam. Neither nitrous oxide nor midazolam alone produced apoptosis, whereas isoflurane did. However, the combination of 2 or more of any of these agents produced significant neurodegeneration, with the "triple cocktail" producing the greatest increase in the number of apoptotic cells. In addition, the triple combination of drugs resulted in persistent memory and learning impairment later in life. This was the first report of behavioural impairment subsequent to anaesthetic exposure and not surprisingly, generated considerable debate within the scientific community about how to interpret the findings.

Collectively, the rodent studies suggest that rats are sensitive to NMDA-antagonists and GABA-agonists and they also imply that anaesthetic agents other than ketamine are neurotoxic to the developing CNS, and may produce neurobehavioural problems later in life. Most worrying is that a combination of drugs commonly used for routine anaesthesia in human infants may produce greater toxicity than individual drugs. The big question is whether or not these findings are clinically relevant to humans.

***Studies in non-human primates***

Studies conducted with cultured monkey frontal cortical neurons found that prolonged exposure of these cells to high concentrations of NMDA-antagonists resulted in apoptosis, but also suggested that there may be dose-related safety margins for ketamine and other agents commonly used in the clinical setting.

Data from initial primate studies conducted in 2005 confirmed that ketamine administered to pregnant females causes enhanced cell death in the foetal brain, consistent with an apoptotic mechanism. However, the apoptosis occurred in different regions of the primate brain as compared to the rodent brain, and there was some evidence suggestive of neuronal compensation. Whether the observed cell death affects overall brain function, or whether the injured brain tissue can recover with no loss of normal function, remains to be seen.

***Where to from here?***

The results of primate studies currently underway with ketamine will impact on how other anaesthetics will be evaluated for safety and efficacy in paediatric patients, particularly new NMDA-antagonist and GABA-agonist agents. In addition, the FDA and National Institute of Health have formally requested paediatric safety studies for a number of commonly used anaesthetic agents, including isoflurane, sevoflurane, desflurane, morphine, fentanyl, remifentanil, propofol and midazolam. As many of these drugs are used in combination, studies will be conducted to determine whether the neurodegenerative effects are additive or synergistic, compared with the individual drugs.

The FDA is also looking into the feasibility of conducting an epidemiological study in neonatal and young paediatric surgical patients, depending on the outcome of the primate studies. Results from the Victorian Infant Collaborative Study Group of 1996 have already suggested that there is an adverse association between the need for surgery requiring general anaesthesia during the primary hospitalisation, and sensorineural outcome in extremely premature or low birth weight infants.

***Summary of long-term effects of anaesthesia in the young***

This brings us to the critical question: How can we know whether or not anaesthetic drugs trigger apoptosis in the vulnerable developing human brain? Rat data provide an imprecise basis at best, and an irrelevant basis at worst, for evaluating human risk. Primate studies have only recently been initiated, but so far, appear to corroborate the rat data. There is another vital issue - what are the alternatives to anaesthesia? Pain and the unchecked stress response are well known to be associated with adverse outcomes. Short-term consequences of withholding anaesthesia include an increased incidence of intra-operative and postoperative complications, leading to poor surgical outcomes. Long-term consequences include prolonged changes in pain sensitivity and pain processing, as well as a variety of neurodevelopmental, behavioural and cognitive deficits manifesting in later childhood.

Currently, it seems clear that *anaesthesia* is still better than *no anaesthesia* if surgery is required. An editorial by Davidson and Soriano raises some questions: "Which anaesthetic is the safest for the developing brain?" So far, most anaesthetics have been implicated as potentially dangerous in rat models. Also: "Should surgery be delayed in infants and young children, and if so, until when?" Given the prolonged human development phase, this would mean months to years, which is usually not a practical option. In the interim, clinicians are advised to minimise exposure to potentially offending drugs when possible, and to consider alternative therapies if available. Research is needed to explore the possibility that use of apoptogenic drugs in obstetric and paediatric medicine may cause alcohol-like effects that have previously escaped detection or have been ascribed to unknown causes.

Finally, whilst the experimental findings in rat models are scientifically sound and merit further investigation, there is no doubt that withholding anaesthesia is potentially harmful to infants and young children, and alleviation of pain and stress during the perinatal period is both essential and humane.

## Long-term effects of anaesthesia in the elderly

### *Cognitive function and anaesthesia*

Elderly surgical patients constitute a unique surgical group, and they require special consideration in order to pre-empt possible long-term adverse effects of anaesthesia. The estimated peri-operative mortality rate in the general population is 1.2% compared with 8.4% in patients over 90 years. These numbers are significantly worse when one considers major surgery alone. One of the most common and serious side-effects in the elderly is postoperative cognitive dysfunction (POCD), as its presence may herald an increase in both morbidity and mortality.

To begin with, it is important to recognise that intellectual decline is a common, although not invariable, finding in the elderly. About 5% of persons older than 65 years will suffer from some degree of dementia, and more subtle cognitive impairment is detectable in over 60% of "normal" elderly people. Cognitive decline can be ameliorated to some extent by remaining intellectually engaged, and even more importantly, through ongoing physical activity. Consequently, there is no such thing as the "typical" older person. Chronological age is not a reliable indicator of cognitive ability.

Until recently, it has been assumed that most anaesthetic agents provide some degree of neuroprotection. Volatile agents, barbiturates and propofol suppress excitatory neurotransmitters like glutamate and AMPA, and potentiate inhibitory ones like GABA, thereby inhibiting ischaemic cascades. They also reduce the cerebral metabolic rate of oxygen consumption ($CMRO_2$). Unfortunately, no agent has ever been shown to have long-term protective effects. Recently, new evidence has come to light casting doubt on the notion of anaesthetic agents as neuroprotective, and suggesting that they may in fact be responsible for a number of long-term adverse sequelae in the elderly surgical patient, including POCD and Alzheimer's disease.

### *Postoperative cognitive dysfunction*

POCD is a deterioration in intellectual function that presents as impaired memory or concentration. It is unique to those who have undergone surgery. The acute manifestation is known as delirium, which is characterised by alterations in attention and consciousness. POCD is often subtle in its presentation and pre- and postoperative neurophysiological testing may be necessary to make the diagnosis.

The incidence is related to the type of surgery, the medications received peri-operatively, and pre-existing comorbidity. The estimated incidence of POCD in the elderly surgical population is 15 – 25% after non-cardiac surgery and 24 – 80% after cardiac surgery, and constitutes a risk factor for poor functional recovery and increased morbidity. Up to 10% of elderly patients will exhibit signs of POCD three months after surgery, placing a huge emotional and financial burden on family members as these patients are invariably unable to live independently. The avoidance and treatment of POCD therefore represents one of the greatest challenges of modern medicine and surgery.

### *The link between postoperative cognitive dysfunction and anaesthesia*

General anaesthesia is a profound form of CNS suppression and is often blamed for POCD, although the clinical evidence for this is surprisingly sparse. Most data indicate that the risk of POCD is identical with regional and general anaesthesia; however, intravenous sedation is often used to supplement regional anaesthesia, making it difficult to isolate the influence of the type of anaesthetic itself. A recent systematic review of anaesthesia techniques and POCD has failed to show a difference.

Anaesthesia, by affecting the release of neurotransmitters within the CNS, could potentially damage memory processes in elderly surgical patients. It is generally believed that the effects of anaesthetic agents do not outlive their pharmacological actions, yet there is increasing evidence that this concept is not true. It seems that long term neurological changes can follow administration of anaesthetic drugs, and the elderly brain may be particularly vulnerable.

Animal studies suggest that even short exposure to a volatile agent can irreversibly alter proteins in the brain. Rats exposed to desflurane anaesthesia were found to have persistent changes in brain cytosolic protein expression, challenging the notion that the effects of volatiles disappear within minutes or hours. Other laboratory studies have found that isoflurane-nitrous oxide anaesthesia without surgery, impairs spatial learning for weeks in aged rats. Since the agents are long cleared from the brain by the time behavioural testing is undertaken, these results suggest that memory is somehow altered in an enduring way by anaesthesia itself. Further confirming these findings, anaesthetic-induced neuroapoptosis occurs in cell culture after exposure to clinically relevant doses of isoflurane, as well as in the brains of old rats after nitrous oxide and ketamine.

The findings from animal studies indicate that general anaesthesia, either by changing or damaging the old brain, could be one of the factors responsible for the development of POCD. However, they do not provide any insight into the pathophysiology of POCD following regional anaesthesia. POCD remains a problem with a multifactorial aetiology, and there is currently no scientific basis for recommending or avoiding a specific anaesthetic agent or technique.

### *Alzheimer's disease (AD)*

Alzheimer's disease is the most common cause of dementia and a prototype of pathological brain ageing. Ten to 15% of persons older than 65 years will develop AD and by 85 years, about 30 – 50% will be afflicted. Brain changes seen in normal ageing are present in an exaggerated form in AD, with loss of brain mass occurring at a rate 2.5 times normal. Cholinergic deficiency is a hallmark of AD, but the leading hypothesis as to the cause centres on an imbalance between the generation and clearance of beta-amyloid protein (BAP). This protein is produced by the proteolytic cleavage of a larger precursor, amyloid precursor protein (APP). Accumulation (also called oligomerisation) of these proteins into so-called amyloid plaques is an early pathological feature in the brain of asymptomatic carriers of gene mutations that predispose to the development of AD. Plaques are widespread in the late stages of this disease. In addition, BAP itself appears to be toxic, and contributes to synapse loss and dysfunction even before plaques are detected.

### *The link between Alzheimer's disease and anaesthesia*

In addition to the concerns over general anaesthesia and POCD, recent reports suggest that Alzheimer's disease is accelerated by anaesthesia and surgery. In fact, although delirium and dementia have long been considered separate conditions, recent evidence has highlighted their inter-relationship. Long-term follow up of patients following coronary artery bypass surgery (CABG) revealed that POCD is present in the following incidences postoperatively: 53% at discharge, 36% after 6 weeks, 24% at 6 months and 42% of patients after 5 years. Three separate studies produced odds ratios of between 1.2 and 1.6 for the association between previous surgery and AD, although none were sufficiently powered to demonstrate statistical significance. In addition, the age of onset of AD was inversely related to the cumulative exposure to anaesthesia before age 50. A recent study also reported that patients having CABG under general anaesthesia were 70% more likely to develop AD compared with those having percutaneous transluminal angioplasty under local anaesthesia. If larger studies confirm these findings, it would imply a 20 to 60% increase in AD as a result of surgery and general anaesthesia.

Eckenhoff et al showed that halothane and isoflurane enhance BAP oligomerisation, potentiate the cytotoxicity of BAP, and increase activity of the APP cleavage enzyme beta-secretase, resulting in apoptosis. This effect occurs even at clinical concentrations of these drugs, but the severity appears to be dose-dependent. Interestingly, in this study, ethanol appeared to inhibit BAP aggregation at low concentrations, suggesting that light to moderate ethanol consumption may reduce the risk of dementia in humans.

Further studies by Xie et al confirmed that clinically relevant concentrations of isoflurane induce apoptosis, alter APP processing, and increase BAP production *in vitro*. The authors concluded that isoflurane contributes to the well-described mechanism of Alzheimer's neuropathogenesis.

These studies provide a pathophysiological basis linking the more acute process of delirium following volatile-based general anaesthesia, with the longer term consequences of dementia.

## Anaesthetic depth as a predictor of mortality

### *Cumulative deep hypnotic time*

Even in the sickest patients, the relationship between anaesthetic management and peri-operative outcome is difficult to determine. As a result, most deaths and complications are attributed to underlying pathophysiology, rather than to anaesthetic management strategies under the control of the anaesthetist in the operating room. The impact of anaesthesia on long-term morbidity is even more difficult to assess.

Recently, the provocative findings of a study by Monk et al has generated much controversy over whether or not anaesthetic technique can influence long-term outcomes after surgery. This was a prospective, observational study of 1064 adult patients undergoing major non-cardiac surgery under general anaesthesia, designed to determine what variables, if any, were associated with mortality in the first year after surgery. One-year mortality was 5.5% in all patients, and 10.3% in patients older than 65 years. Not surprisingly, patient comorbidity and intra-operative hypotension were identified as significant independent predictors of mortality. However, the study describes another factor that is associated with increased 1-year mortality: the cumulative deep hypnotic time. This refers to the amount of time that patients were exposed to anaesthesia at a Bispectral Index (BIS) value of < 45, bearing in mind that the BIS value was only recorded and was not seen by the anaesthesiologist. Unexpectedly, there was a 24% increased risk of mortality at 1-year for every hour spent at a BIS value of < 45.

For many patients, awareness is the primary concern relating to anaesthesia, prompting anaesthetists to err on the side of deep anaesthesia rather than risk intra-operative awareness. In addition, anaesthetic depth is often used as a tool to provide better control of arterial blood pressure, or other haemodynamic variables. In this study, Monk suggests that prolonged, deep anaesthesia may have a negative impact on patient outcome and should perhaps be minimised in order to prevent unanticipated complications and morbidity. Importantly, total duration of anaesthesia itself did not affect outcome, only increasing duration at deep levels of anaesthesia had an effect.

A number of methodological flaws and limitations have been identified in Monk's study; however, the findings are indirectly supported by another recent study. Lennmarken et al, in a preliminary report, showed that advancing age and low intra-operative BIS levels were associated with increased postoperative mortality. In this study, data from over 4000 patients undergoing non-cardiac surgery was analysed to ascertain factors associated with increased mortality. Cumulative deep hypnotic time conferred a 20% increased risk of 1-year mortality per hour spent at a BIS below 45.

Monitoring hypnotic depth with techniques such as the BIS index yields clinically relevant information, because routine anaesthetic practice results in significant variability in dosing and patient response. Elderly patients in particular require less anaesthetic than their younger, healthier counterparts, and BIS monitoring may be able to detect differences in dosing. It has been suggested that the reason that previous studies failed to detect a long-term effect on outcome is because the type of anaesthetic has been studied, rather than the amount of anaesthetic or the effect on the brain. Despite questions about the study designs and the value of cumulative deep hypnotic time as a predictor of mortality, these findings warrant further investigation. Furthermore, they have prompted some authorities to suggest that BIS monitoring should be considered essential when anaesthetising elderly or very sick patients.

### *How does deep anaesthesia affect mortality?*

The majority of deaths in Monk's study were attributed to cancer (52% of deaths at 1-year) and cardiovascular (17%) causes. The inflammatory response has been linked to atherosclerosis, cancer and Alzheimer's disease, and has been labelled "the silent killer". The authors postulate that prolonged, deep anaesthesia may alter the inflammatory response in high-risk patients, and predispose them to worsened outcomes by accelerating pre-existing or latent disease processes. This will be discussed in more detail in the following section. As these studies are observational in design, it is important to note that associations reflect correlation and not necessarily causation.

## Anaesthetics and immune function

It is generally believed that present-day anaesthesia is so safe that little benefit would be obtained from advances in the field, and that the effect on short-term morbidity and mortality would be difficult to prove in any study. However, a new body of evidence has emerged suggesting that peri-operative management of the surgical patient may affect outcome for months or even years after surgery. Although the causes of death for longer periods are frequently not available, an increased risk for cancer-related and cardiovascular deaths has been put forward in the study that was published in 2005 by Monk et al. Anaesthetic-induced alteration in immune function has been implicated as one of the factors contributing to these findings.

Such is the level of interest and concern about the effects of anaesthesia on the peri-operative inflammatory response, that the APSF devoted 2 of the 4 sessions to this topic at its specially convened meeting on anaesthesia and long-term outcomes.

In the normal individual, surgery induces a pro-inflammatory reaction to limit infection and also provides a suitable environment for tissue healing and repair. Persistent and uncontrolled secretion of these pro-inflammatory cells is implicated in the pathophysiology of systemic inflammatory response syndrome (SIRS). In response to this pro-inflammatory reaction, the body mounts an active anti-inflammatory response, which is not just a "burnout" of the pro-inflammatory functions, but rather involves specific resolution mediators known as resolvins. Resolvins promote and speed up the resolution process, and have been identified as the active ingredients of the beneficial effects of Omega3 fish oils. If resolution is sufficiently exuberant, it will manifest as anergy and increased susceptibility to infection. In addition, it may dampen the body's own anti-inflammatory processes, thereby allowing latent inflammation to supervene. This may explain the manner in which anaesthesia encourages more rapid progression of atherosclerosis. Optimal prevention and cure of illness therefore requires a balance between pro- and anti-inflammatory reactions.

Volatile agents are dose-dependent suppressors of the immune response *in vitro*, whereas clinical anaesthesia has more variable effects. Compared with total intravenous anaesthesia (TIVA),

balanced inhalational anaesthesia is a more potent inhibitor of immune cell function. As yet, there is no human data to suggest that the immunosuppressive effects of volatile agents are harmful to patients. On the other hand, the anti-inflammatory and cardiac conditioning effects of volatile anaesthetics may produce improved outcome in high-risk cardiac patients.

In the ICU setting, both propofol and midazolam have been shown to inhibit immune function, particularly after prolonged infusion. This may be beneficial in the patient with SIRS, but may lead to an increased risk of nosocomial infections in critically ill individuals, and may ultimately lead to septic shock and multiple organ failure.

Morphine is well accepted as being a suppressor of innate and adaptive immunity by interacting with opioid receptors on immune cells. In contrast, synthetic opioids (e.g. fentanyl and sufentanil) have considerably weaker interactions with leukocyte opioid receptors and consequently have a less pronounced effect on immunity.

Local anaesthetics reduce inflammation by inhibiting the inflammatory cascade at multiple levels, and have demonstrated beneficial effects in the clinical management of various acute and chronic inflammatory disorders, such as myocardial infarction and inflammatory bowel syndrome. However, recent reports caution that local anaesthetics may also increase the risk of pre-existing bacterial infections through their profound anti-inflammatory action.

In summary, anaesthetics directly cause immune suppression by influencing the function of immunocompetent cells. As the optimal prevention and cure of illness requires a balance between pro-inflammatory and anti-inflammatory reactions, the immuno-modulatory effects of some anaesthetics represent a double-edged sword. Further studies are needed to evaluate the relationship between inflammation and long-term outcomes after surgery and anaesthesia. Meanwhile, anaesthetics and sedatives should be administered with careful regard to their potential effects, the clinical scenario, and the immune status of the critically ill patient.

## Long-term effects of occupational exposure to volatile agents

### *Sensorimotor impairment*

Some of the more common complaints of operating room personnel exposed to halogenated volatile agents include disorientation, fixated vision, vertigo, headaches, mood disorders, slow reaction time and reduced cognitive efficiency. In addition, muscle weakness, numbness and tingling have been reported. These indicators of sensorimotor dysfunction may lead to an increased risk of occupational accidents such as needle stick injuries. Thus contamination of the theatre environment is an issue relevant to all anaesthetists.

Vouriot et al evaluated the chronic effects of exposure to anaesthetic gases (nitrous oxide, sevoflurane, desflurane and isoflurane) on postural control in theatre personnel. The study group included operating room personnel occupationally exposed to gases for at least 5 years. Both static and dynamic balance control were significantly impaired in the study group compared to controls, particularly in the eyes closed condition. The central nervous system depressant effect of anaesthetic agents appears to affect the selection and integration of sensory cues, as well as the adaptation of motor responses to destabilisation, thus impairing the accuracy of motor skills.

### *Genetic damage in theatre personnel*

Using identification of chromosomal aberrations in peripheral blood lymphocytes, Rozgaj et al showed that surgeons, anaesthetists and theatre nursing staff are all at risk of sustaining chromosomal damage correlating with the duration and degree of occupational exposure. These findings were confirmed by Hoerauf and colleagues – there was a significantly higher incidence of sister chromatid exchanges, indicative of mutagenicity, in workers exposed to anaesthetic gases than in non-exposed controls. The measured differences were comparable to smoking 11 – 20 cigarettes a day. Whilst the clinical relevance of increased chromosomal breaks remains unknown, the possible synergistic action of anaesthetic agents and ionising radiation is a concern for all staff regularly exposed to both.

Whether or not genetic damage could result in cancer or other unfavourable health outcomes remains unclear. Provided an otherwise healthy subject has sufficient DNA repair mechanisms and no other health risks (e.g. smoking, immune deficiency, or other potential genetic hazards), these genetic changes may be both reversible and inconsequential. Currently, further investigation is required to clarify the long-term consequences of this damage.

### *Effect of volatile agents on oxidative stress*

Inhalational agents are a source of reactive oxygen radicals, and long-term occupational exposure in theatre personnel may result in depletion of antioxidant enzymes. Free radicals may cause damage to cellular DNA and have adverse effects on immunity. A study by Turkan et al looked at the plasma and erythrocyte levels of the major antioxidant enzymes – superoxide dismutase (SOD) and glutathione peroxidase (GSH) – and their cofactors, namely zinc, selenium and copper, in chronically exposed anaesthesia personnel, and compared them to controls. The study group included staff who had worked in the operating theatre a minimum of 6 hours daily for at least 3 years. They found that antioxidant and trace element levels were significantly lower in the study group, but because single anaesthetic agents were not used in the theatres, they were unable to identify which agent, if any, was responsible for the reduction. This was despite the use of closed anaesthesia systems and passive scavenging of gases. The authors recommended minimising exposure to inhalational agents by means of scavenging, closed systems, low-flow anaesthesia and good anaesthetic technique. In addition, they recommended that operating room personnel should take antioxidant supplements.

### *Neurotoxicity of inhalational agents*

Studies have suggested that exposure to organic solvents, including volatile anaesthetic agents, may be a risk factor for multiple sclerosis (MS), possibly in combination with genetic and other environmental factors. Landtblom et al found that the cumulative incidence ratio of MS was increased in female nurse anaesthetists in relation to other nurses, although this was not statistically significant. However, there was a significantly increased risk of developing MS compared to teachers. This is interesting in the context of previous observations of organic solvents in general as a potential risk factor for MS.

### *Reproductive health in theatre personnel*

There is reasonably convincing evidence of an increased risk of spontaneous abortion among females occupationally exposed to anaesthesia, although there is no particular reason to believe that this has anything to do with exposure to trace amounts of anaesthetic gases. The unique emotional and physical rigours of theatre work, for example, might easily be responsible.

There is no evidence for excess spontaneous abortion rates among wives of exposed males, for an increase in malformation or stillbirths among the offspring of exposed females, or for more low birth weight babies. In addition, sex ratio at birth is the same as non-exposed controls, and infertility rates are also similar.

***Cancer***

A number of studies have investigated whether or not there is an increased incidence of tumour related morbidity or deaths amongst anaesthetists. Some have suggested that cancers of the lymphoid and reticulo-endothelial systems, such as lymphoma, leukaemia and multiple myeloma, are more prevalent amongst this group. However, the general consensus is that there is no convincing evidence that any form of cancer is an occupational hazard of anaesthesia.

***Immunological effects of exposure to volatile agents***

Peric et al investigated the effects of occupational exposure to nitrous oxide and halothane in the setting of improperly ventilated operating theatres. The staff had been complaining of weakness, fatigue and recurrent infections. In addition, reduced peripheral blood leukocyte counts had been found on routine testing. During exposure, the number of white blood cells was significantly reduced, but recovered to normal levels after a 4-week holiday. It was impossible to assess the relative influence of halothane and nitrous oxide on the findings. Since the gas concentrations were many times higher than the allowed maximum, the authors noted that when scavenging is adequate, such findings are not reported in other studies.

***What is the relationship between the practice of anaesthesia and life expectancy?***

There is considerable speculation regarding the effect that an operating room environment has, with its exposure to stress and anaesthetic agents, on the life expectancy of those who work there. While earlier retrospective surveys of anaesthesiologists found that the death rate was less than the general male population, a preliminary report of the most recent comparison of anaesthesiologists practicing during 1976-1996 with a random sample of internists demonstrates conflicting results. When matched for sex, decade of birth, and other factors, no difference was observed in overall mortality or death due to cancer or heart disease. However, drug related deaths (RR = 2.75), HIV-related deaths (RR = 1.78), and suicides (RR = 1.45) were more common in anaesthesiologists. These findings are consistent with recent reports of higher illicit substance abuse and addiction among anaesthesiologists, and the use of invasive techniques in high infectious risk patients.

In England, death in post and early retirement due to ill health has also been noted to be significantly increased in consultant anaesthesiologists, when compared with control consultants in five other medical specialties. However, since the data was confidential, the nature of the ill health or deaths is unknown.

Overall, these limited data suggest that an increased mortality and shorter life expectancy may indeed exist! However, as these studies have been observational in nature with poor controls, further work will have to be conducted.

**Conclusion**

The long-term effects of general anaesthesia on brain function represent a burgeoning area of interest in clinical research. Long-term outcome is a new safety concern, since a number of recent studies suggest that peri-operative events and care decisions may affect the patient adversely months or even years after surgery. This is particularly true of patients at the extremes of age who appear to be more vulnerable to the subtle adverse effects of general anaesthesia. It remains to be seen whether or not deep anaesthesia is an independent predictor of postoperative mortality.

A number of mechanisms have been proposed for these unanticipated outcomes, including the effect of anaesthetic agents on the immune system and inflammation, and anaesthetic-induced apoptosis. So far, the available information is extremely sparse, complicated and has many limitations, but should be pursued until its conclusion.

Finally, the risk of long-term adverse effects of occupational exposure to anaesthetic agents is very small. **SAJAA**

**Bibliography**:


1. Schneider H. Psychodiagnostic study results following chronic halothane exposure - a report of experiences. Z Gesamte Hyg 1986; 32:104-6.
2. Vouriot A, Gauchard GC, Chau N, et al. Chronic exposure to anaesthetic gases affects balance control in operating room personnel. NeuroToxicology 2005; 26:193-8.
3. Rozgaj R, Kasuba V, Peric M. Chromosome aberrations in operating room personnel. Am J Ind Med 1999; 35:642-6.
4. Turkan H, Aydin A, Sayal A. Effect of volatile anaesthetics on oxidative stress due to occupational exposure. World J Surg 2005; 29:540-2.
5. Landtblom AM, Tondel M, Hjalmaarsson P, et al. The risk for multiple sclerosis in female nurse anaesthetists: a register based study. Occup Environ Med 2006; 63:387-9.
6. Lewis MC, Nevo I, Paniagua MA, et al. Uncomplicated general anaesthesia in the elderly results in cognitive decline: Does cognitive decline predict morbidity and mortality? Medical Hypotheses 2007; 68:484-92.
7. Crosby G. Anaesthesia, aging and the brain: clinical implications of an evolving science. ASA Annual Refresher Course Notes 2006; pg 302.
8. Gaba DM et al. APSF Workshop on Long Term Outcomes - Final Report. *http://www.apsf.org/assets/Documents/APSF_LTO_Wkshop_Report.pdf*
9. Hoerauf K, Lierz M, Wiesner G, et al. Genetic damage in operating room personnel exposed to isoflurane and nitrous oxide. Occup Environ Med 1999; 56:433-7.
10. Vessey MP. Epidemiological studies of the occupational hazards of anaesthesia – a review. Anaesthesia 1978; 33:430-8.
11. Monk T, Saini V, Weldon BC, Sigl JC. Anaesthetic management and one-year mortality after non-cardiac surgery. Anesth Analg 2005; 100:4-10.
12. Homburger JA, Meiler SE. Anaesthesia drugs, immunity and long-term outcome. Curr Opin Anaesthesiol 2006; 19:423-8.
13. Drage M. Caution in the use of lidocaine infusion in the surgical patient. Anesth Analg 1998; 87:1213.
14. Kelbel I, Weiss M. Anaesthetics and immune function. Curr Opin Anaesthesiol 2001; 14:685-91.
15. Davidson A, Soriano S. Does anaesthesia harm the developing brain – evidence or speculation? Paediatric Anaesthesia 2004; 14:199-200.
16. Ikonomidou C, Bosch F, Miksa M, et al. Blockade of NMDA receptors and apoptotic neurodegeneration in the developing brain. Science 1999; 283:70-4.
17. Scallet AC, Schmued LC, Slikker W, et al. Developmental neurotoxicity of ketamine: morphometric confirmation, exposure parameters, and multiple fluorescent labelling of apoptotic neurons. Toxicol Sci 2004; 81:364-70.
18. Mellon RD, Simone AF, Rappaport, BA. Use of anaesthetic agents in neonates and young children. Anesth Analg 2007; 104:509-20.
19. Crews FT, Mdzinarishvili A, Kim D, et al. Neurogenesis in adolescent brain is potently inhibited by ethanol. Neuroscience 2006; 137:437-5.
20. Jevtovic-Todorovic V, Hartman RE, Izumi Y, et al. early exposure to common anaesthetic agents causes widespread neurodegeneration in the developing rat brain and persistent learning deficits. J Neuroscience 2003; 23:876-82.
21. Victorian Infant Collaborative Study Group. Surgery and the tiny baby: Sensorineural outcome at 5 years of age. J Paediatr Child Health 1996; 32:167-72.
22. Soriano SG, Anand KJ. Anaesthesia and brain toxicity. Curr Op Anaesthesiol 2005; 18:293-7.
23. Anand KJ, Soriano SG. Anaesthetic agents and the immature brain: are these toxic or therapeutic agents? Anesthesiology 2004; 101:527-30.
24. Koerner IP, Brambrink AM. Brain protection by anaesthetic agents. Curr Opin Anaesthesiol 2006; 19:481-6.
25. Eckenhoff RG, Johansson JS, Wei H, et al. Inhaled anaesthetic enhancement of amyloid-beta oligomerisation and cytotoxicity. Anaesthesiology 2004; 101:705-9.
26. Xie Z, Dong Y, Maeda U, et al. Isoflurane-induced apoptosis: a potential pathogenic link between delirium and dementia. J Gerontology 2006; 12:1300-06.
27. Xie Z, Dong Y, Maeda U, et al. The common inhalation anaesthetic isoflurane induces apoptosis and increases amyloid beta protein levels. Anesthesiology 2006; 104:988-94.
28. Newman MF, Kirchner JL, Phillips-Bute B, et al. Longitudinal assessment of neurocognitive function after coronary artery bypass surgery. N Engl J Med 2001; 344:395-402.
29. Lee TA, Wolozin B, Weiss KB, et al. Assessment of the emergence of Alzheimer's disease following coronary artery bypass graft surgery or percutaneous transluminal angioplasty. J Alzheimer's Dis 2005; 7:319-24.
30. Lennmarken C, Lindholm M, Greenwald SD, et al. Confirmation that low intra-operative BIS levels predict increased risk of postoperative mortality. Anesthesiology 2003; 99:A303.
31. Fong HK, Sands LP, Leung JM. The role of postoperative analgesia in delirium and cognitive decline in elderly patients: a systematic review. Anesth Analg 2006; 102:1255-66.
32. Wu CL, Hsu W, Richman JM, et al. Postoperative cognitive function as an outcome of regional anaesthesia and analgesia. Reg Anesth Pain Med 2004; 29:257-68.
33. Futterer CD, Maurer MH, Schmitt A, et al. Alterations in rat brain proteins after desflurane anaesthesia. Anesthesiology 2004; 100:302-8.
34. Ikonomidou C, Bittigau P, Koch C, et al. Neurotransmitters and apoptosis in the developing brain. Biochem Pharmacol 2001; 62:401-5.
35. Peric M, Vranes Z, Marusic M. Immunological disturbances in anaesthetic personnel chronically exposed to high occupational concentrations of nitrous oxide and halothane. Anaesthesia 1991; 46:531-7.