

SUPPLEMENT 1

BACKGROUND TO POSTOPERATIVE DELIRIUM AND POSTOPERATIVE COGNITIVE DYSFUNCTION

Changes in cognition are known to follow anaesthesia and surgery. Although simple survival was the prime 19th and early 20th century outcome for invasive procedures, a link was none-the-less observed with adverse cognitive outcomes. Historical reports of 'insanity' or 'weak mindedness' after anaesthesia appeared 40 years after the first anaesthetic was administered and anecdotal and retrospective reports have implicated anaesthesia ever since. With the advent of cardiac surgery in the 1970s, clinicians became aware of cognitive changes after cardiac surgery using cardiopulmonary bypass, an operation that was often undertaken in the elderly.

NEUROLOGICAL INJURY AFTER ANAESTHESIA AND SURGERY

The exact cause of neuropsychiatric decline after anaesthesia and surgery is unknown. Focal neurological injury may be the result of definitive damage to specific neurons caused by emboli, regional ischemia or focal haemorrhage. Recently, the use of imaging techniques such as PET and diffusion-weighted MRI have been able to identify new lesions or transient ischaemic attack following many interventions.[1] These may result in clinically manifest stroke or transient ischaemic attack or alternatively have no adverse clinical outcomes. Although it is conceivable that direct neurological injury may contribute to neuropsychiatric change, evidence suggests that cognitive decline may be the result of other as yet unidentified factors. There appears to be no relationship between embolic count and the incidence of postoperative cognitive dysfunction (POCD).[2]

It should be noted from the outset that invasive diagnostic procedures and surgery always requires some form of accompanying anaesthesia, making it difficult to attribute neuropsychiatric consequences to either component. At the clinical level it will never be possible to completely separate anaesthesia from surgery. It may not be possible to get Institutional Review Board (IRB) approval to administer anaesthesia alone for the purposes of researching cognition and it is morally unacceptable (even criminal) to administer surgery without anaesthesia.

DELIRIUM

The diagnostic criteria for delirium in DSM-5 are[1]:

- a. A disturbance in attention
- b. The disturbance develops over a short period of time, represents a change from baseline attention and awareness, and tends to fluctuate in severity during the course of the day
- c. An additional disturbance in cognition (e.g. memory deficit, disorientation, language, visuospatial ability, or perception)

- d. The disturbances in a or c are not better explained by another pre-existing, established or evolving neurocognitive disorder and do not occur in severely reduced level of arousal such as coma
- e. There is evidence from the history, physical examination, or laboratory findings that the disturbance is a direct consequence of another medical condition, substance intoxication or withdrawal or exposure to a toxin or is due to multiple aetiologies.

EMERGENCE 'DELIRIUM' OR EMERGENCE EXCITEMENT

In the operating room environment, the most noticeable form of 'delirium' is emergence excitement or agitation. This is observed immediately on emergence from general anaesthesia and resolves within minutes to hours. The incidence is about 3% in adults[2] but is more common in children and younger adults. It is associated with emerging from anaesthesia and often is triggered by factors that contribute to agitation, confusion and irritation such as the presence of an endotracheal tube, pain, disorientation, or urinary irritation from full bladder or catheter.[3] Many of these precipitating factors can be readily identified and managed. Emergence 'delirium' in the paediatric population has been demonstrated to be associated with preoperative anxiety and certain anaesthetic techniques, and responds to behavioural preparation, preoperative sedation, and careful anaesthetic management.[4] Although agitation can be dramatic to observe (and can lead to dislodging intravenous drips and monitoring), it is generally of short duration, is often self-limited or it can be managed with appropriate analgesia or sedation. Furthermore emergence excitement is usually a form of transition from anaesthetic state to oriented and responsive consciousness and this is not preceded by a period of cognitive clarity. This state does not fit with other definitions of delirium or cognitive impairment and there are no known long term sequelae to this condition alone.

POSTOPERATIVE DELIRIUM (POD)

Postoperative delirium is a serious problem because of its duration, high incidence in the elderly, and associated adverse outcomes.[5] It exists in both hyperactive (agitated) and hypoactive forms, or as a combined presentation. Compounding clinical care and research is a tendency for POD to go unrecognized, especially when patients have the hypoactive form. After surgery, the incidence of delirium in the elderly is high and ranges from 11-53%. It is also extremely common in the intensive care with an incidence of 19-87%.[1, 6]

Postoperative delirium is associated with poor clinical outcomes including prolonged hospitalization, and death. [7] It can lead to longer term cognitive impairment and loss of function.[8, 9] Not surprisingly, in addition to these adverse outcomes, it is also associated with significant economic costs.[6]

Patients with POD may emerge from anaesthesia and surgery normally and may be lucid before POD manifests over the following 24-72 hours. On the other hand emergence delirium is associated with a greater incidence of POD over the ensuing days.[10]It has an acute onset and a variable course. In contrast to agitation on emergence (or emergence 'delirium' – see above), POD usually affects the elderly, where it often imposes on existing or new cognitive problems. The incidence of POD after repair of fractured hips is over 50% and it is also very common after abdominal, cardiac and peripheral vascular surgery. [5] These surgeries are usually performed in the elderly. In addition to the type of surgery, a number of preoperative risk factors

have been identified. These include prior cognitive impairment, poor physical function, alcohol abuse, bladder catheter, psychoactive drugs, restraint, polypharmacy and dehydration. In several recent studies of elderly patients followed for two years after surgery, patients who developed POD were more likely to die, be diagnosed with dementia or mild cognitive impairment (MCI), and require institutionalisation [8, 11].

CAUSE

The precise cause of POD is unknown, although disturbances in neurotransmitter balance (e.g. cholinergic, dopaminergic and GABA) have been proposed as mechanisms. Triggers for POD have been labelled as multifactorial. It results from the interaction between exposure to precipitating factors and patient vulnerability. The strongest predictor of POD is impaired preoperative cognition.[12] Although regional anaesthesia has the potential to reduce this exposure, studies of general versus regional anaesthesia have not demonstrated a reduction in delirium except possibly with spinal anaesthesia in the repair of fractured neck of femur. This may be in part due to the fact that regional anaesthesia is usually accompanied by sedation.[13] It should be noted that light sedation is associated with a decreased incidence of delirium than deeper sedation.[14]

Both anaesthesia and surgery present a number of acute precipitating factors. Anaesthesia exposes the patients to a range of centrally acting drugs which all have the potential to interfere with neuronal systems. The surgery itself initiates an acute stress response activating a multitude of inflammatory mediators, including kinins and interleukins, which are now known to communicate with the brain via a number of mechanisms.[15] There is the trigger of postoperative pain and the drugs used to treat this and additionally the elderly may be subject to a variety of physiological perturbations, ranging from dehydration to transient hypotension, any of which may contribute to the problem. Finally, elderly patients are susceptible because of a high prevalence of cognitive impairment or dementia, as well as functional and sensory impairment (auditory and visual).

POSTOPERATIVE COGNITIVE DYSFUNCTION

CARDIAC SURGERY

In 1982, Savageau and colleagues introduced neuropsychological testing to investigate cognitive changes after cardiac surgery.[16] They used Trail Making Tests and the Visual Reproduction (VR) Test of the Wechsler Memory Scale (WMS). Postoperative decrements greater than one standard deviation were observed in each of the four scores derived from this testing in 11% to 17% of the patients. The term neuropsychological dysfunction was introduced to describe these changes.

In 1986, a Finnish study used a battery of seven neuropsychological tests in 44 patients undergoing valve replacement surgery with cardiopulmonary bypass.[17] Five year follow-up showed a distinct interrelationship between the clinical outcome immediately after operation and the long-term neuropsychological course, which was measurable 5 years after the surgery. It was noted that the observed clinical signs of central nervous system dysfunction were very mild in the majority of cases and that their detection would not have been likely without thorough and repeated clinical investigation which was compared to baseline performance.

In 1987 Shaw and colleagues [18] used a battery of ten neuropsychological tests two days before and seven days after cardiac surgery. The tests were chosen to assess a

wide range of cognitive attributes. A patient was considered to show significant deterioration on a test if the postoperative score dropped by >1 SD (of the whole group change score) below their individual pre-operative score. They defined moderate or severe degrees of neuropsychological dysfunction as impairment on 3 or more subtests and mild as a decrement in one subtest. Their results showed that after cardiac surgery, neuropsychological change was evident in 79% of cardiac patients compared with 31% of surgical control patients (patients undergoing vascular surgery without cardiopulmonary bypass) at day seven. They concluded “CNS complications occur with much greater frequency and severity after heart surgery with cardiopulmonary bypass” (although it should be noted the vascular controls also suffered from neuropsychological change, albeit with a lesser frequency). The severity of change was often not of sufficient severity to cause serious concern to the patients or to interfere with their everyday activities in the hospital environment.

This investigation stimulated much research into identifying which particular aspect of cardiopulmonary bypass was responsible for cognitive decline. Proposed factors included the type of oxygenator, gaseous emboli, pump flow rates, pH management, perfusion pressures, arterial line filtration, type of pump, particulate emboli, and temperature. However this flurry of research activity was often poorly organised, used disparate methodology and small numbers of patients. A variety of neuropsychological tests were utilised in a variety of test batteries, administered at various time intervals and differing criteria were used for defining neuropsychological dysfunction.[19] In an attempt to encourage some consistency, a Consensus Statement of experts was published in 1995. Although 4 tests were recommended, no specific test or battery was stipulated, nor was standard criteria for decline, but test requirements were well described. A further statement in 1997 highlighted the differences between group mean results and individual test outcomes,[20]

In 2001, Newman and colleagues used seven neuropsychological tests which were analysed by primary component analysis to establish a composite cognitive index for four cognitive domains.[21] A decline of greater than 1 SD in any of the four cognitive domains was defined as neurocognitive dysfunction or postoperative cognitive dysfunction (POCD). They reported the incidence of cognitive decline as 53 percent at discharge, 36 percent at six weeks, 24 percent at six months, and 42 percent at five years.

In 2000, despite the disparity between investigations, a systematic review of neurocognitive dysfunction after coronary artery bypass surgery found an incidence of 22.5% (95% confidence interval (CI), 18.7 to 26.4) of patients with a cognitive deficit (a decrease of at least 1 standard deviation in at least two of nine or ten tests) at 2 months after the operation.[22] The neuropsychological testing used varies from simple mini-mental state examination (MMSE)[23] scores to complex batteries of neuropsychological tests and even computerized batteries.[24] Moreover, there are a variety of different criteria for defining dysfunction. In the absence of a control group, early investigations often use a decline of ≥ 1 SD (from mean baseline score in each test) as a cut-off for decline in an individual test. In response to calls for appropriate control groups, [25, 26] investigators began to use controls to account for both known and unknown confounders in addition to individual change. When control groups were used, the calculation of decline was referenced to the expected change over time and with repeated testing in the control group using one of several formulae for the Reliable Change Index (RCI).[27] In addition to the use of different methods of

calculating decline in an individual test and calculating overall decline, investigators have introduced a number of other variables, which makes comparison of results difficult. These include variability in the number of tests administered and the number of tests required for decline to classify an individual as having POCD [28]. Additionally, postoperative testing was undertaken at variable time intervals after surgery. The end result is that it has been difficult to form a standardized definition of POCD because of the heterogeneity of methods to both measure and analyse cognitive change.

In addition to variable methodology, diverse terminology has evolved as different investigators labelled their findings after neuropsychological testing. Thus neurobehavioral, neuropsychological, neuropsychiatric, cognitive, central nervous system, have all been adjectives used in combination with an equal variety of nouns, including change, deficit, and dysfunction.

NON CARDIAC SURGERY

In 1998, a large European trial published in the Lancet (called the International Study for POCD – ISPOCD), tested for cognitive dysfunction in over 1000 patients (aged >60 y) undergoing a variety of major non-cardiac surgical procedures.[29] Cognitive dysfunction was found in 25.8% [95% CI 23.1-28.5]) of patients 1 week after surgery and in 9.9% [8.1-12.0]) 3 months after surgery, compared with 3.4% and 2.8%, respectively, of UK controls (p<0.0001 and p=0.0037). Age was the major association with cognitive dysfunction. This trial was pivotal for a number of reasons.

1. It returned the focus to include non-cardiac surgery in the elderly (in the years prior, cardiopulmonary bypass was the main feature of perioperative cognitive studies)
2. It monitored blood pressure and hypoxemia in the perioperative period and assessed the impact on POCD - eliminating these physiological perturbations as significant contributory factors in POCD.
3. It found an association between age and education for early POCD and age for late POCD (and thus suggested a similarity to cognitive decline in population studies unrelated to anesthesia and surgery).
4. It used a matched control group to calculate the incidence of POCD.
5. It used a modified reliable change index (RCI) to calculate decline in individual test performance. Change scores in the control group were subtracted from the patient change score to account for expected change (e.g. learning effect) and this was divided by the SD of the change in the control group:

$$RCI = (\Delta X - \Delta X_c) / SD(\Delta X_c)$$

ΔX : difference in preoperative score and postoperative score

ΔX_c : mean of difference in control group preoperative and postoperative scores

$SD(\Delta X_c)$: standard deviation of the control group change;

6. It used strict criteria to define POCD. The RCI is similar to a Z score. A decrease ≤ 2 was taken as the cut-off because less than 2.5% of the normal population would lie below this point – robustly indicating severe impairment.

POCD was defined when two or more tests fell below the cut-off or if the combined Z-score fell below this cut-off. The definition thus accounted for specific falls in individual cognitive tests or a general fall in all the tests.

In the USA, Monk and colleagues confirmed many of the findings of the ISPOCD study [30]. They investigated 365 patients (aged >60 y) undergoing non-cardiac surgery using a similar study design to the ISPOCD group. They found an incidence of POCD of 41.4% [95% CI: 36.2 to 46.7] at discharge and 12.7% [95% CI: 8.9 to 16.4] at 3 months. Again age and education were associated with POCD. Patients with POCD at hospital discharge were more likely to die in the first 3 months after surgery and within the first year if they had POCD at 3 months. This was the first study to associate mortality with POCD.

POCD has clinical impact. Although POCD is classified purely by cognitive testing, it is associated with definite adverse consequences in the short term. These include increased length of hospital stay and increased mortality. Patients with POCD after cardiac surgery were more likely to have increased length of hospital stay than those without POCD (No POCD: 7.1 ± 3.4 days; POCD 8.3 ± 4.1 days ($p=0.02$)).[31] As noted above, Monk and colleagues found patients with POCD at hospital discharge were more likely to die in the first 3 months after surgery (6.5%) than those without POCD (3.4%) ($P = 0.02$). Likewise, patients who had POCD at both hospital discharge and 3 months after surgery were more likely to die in the first year after surgery than those without POCD (10.6% vs 2.1%) ($P = 0.02$).

LONG TERM POCD

The majority of studies after anaesthesia and surgery have focused on early assessment (typically at seven days, which is often before discharge, and therefore is logistically straightforward) and 3 months (a time when the effects of hospitalization and perioperative drugs have passed). There have been at least 5 studies which examined cognitive function several years after cardiac surgery.[32] The results of these are suggestive of a long term impact. Selnes and colleagues found a moderate decrease in cognitive function at 5 years.[26] At 6 years after anaesthesia and surgery they observed, using pooled analysis, that decline did not differ from a medical intervention group. [33] Newman and colleagues found an incidence of POCD of 42% at 5 years (associated with early POCD) and Stygall and colleagues also reported decline.[34] At the time of writing there are no prospective long-term follow-ups after non-cardiac surgery. The ISPOCD group followed up a small subgroup for 1 year. They found an incidence of POCD of 10.4% which was almost identical to a non-operative control group.

QUALITY OF LIFE OUTCOMES

POCD, which is defined using cognitive testing, may have little impact on measures of an individual's daily function. Impact on daily life may be a more relevant outcome. Newman et al studied quality of life 5 years after cardiac surgery and found lower 5-year overall cognitive function scores were associated with lower general health and a less productive working status.[35] Steinmetz and colleagues used administrative databases to follow a subgroup from the ISPOCD study for a median follow-up time of 8.5 years and identified an association of POCD with increased mortality, risk of leaving the labor market prematurely, and dependency on social transfer payments.[36]

LIMITATIONS OF STUDIES OF POCD

Although most studies have assiduously confined patient inclusion criteria to those aged ≥ 60 y (the group at risk), there has been little attention paid to the status of pre-operative cognition. Individuals with MMSE < 24 were excluded from the studies by Moller et al [29] and Monk et al [37], but otherwise no measure or classification of preoperative cognitive status was included. This is an important issue because the prevalence of cognitive impairment in the general population aged ≥ 65 y may be as high as 50%. A retrospective analysis of individuals with MCI suggested that they were prone to develop POCD; although the criteria used were not of a high standard.[38]

DOES TYPE OF ANAESTHETIC AFFECT POCD?

The implicit assumption in this question assumes that the anaesthetic is the cause of the problem. However, as stated at the outset, anaesthesia is always accompanied by surgery.

The assumption that anaesthesia causes POCD rests on the fact that the target organ for anaesthesia is the brain. Anaesthesia induces a (presumably) reversible medical coma and acts directly on neuronal activity. A simplistic deduction would be to conclude that since POCD is a consequence of impaired neuronal activity or impaired neuronal recovery from unconsciousness, that the anaesthetic agent is the culprit. This assumption completely ignores the fact that surgery itself is not benign. Surgery activates a diverse range of inflammatory processes, which impact on every system in the body, including the brain.

Although some laboratory and animal data suggests that inhalational anesthetic agents may be implicated in the Alzheimer's pathological process[39, 40], and one rudimentary clinical study supports this[41], there is no evidence that any particular anesthetic agent is implicated.

It has been suggested that the use of regional anaesthesia (e.g. spinal or epidural) which avoids centrally acting potent inhalational and intravenous anesthetic agents may decrease the incidence of POCD. A trial investigating this issue enrolled 428 patients and found an incidence of POCD at 3 months of 14.3% (95% CI: 9.5 to 20.4) after general anesthesia which was not significantly different from regional anesthesia (13.9%; 95% CI: 9.0 to 20.2).[42] A systematic review also found no difference in the incidence of POCD between regional and general anesthesia.[43] However, intravenous sedatives and strong postoperative analgesics (including opioids) are often given with regional anaesthesia to treat the patient. Since neither sedatives nor strong analgesics were consistently excluded from the regional groups in these trials, it is possible that these centrally acting drugs were involved in POCD. In 2014, a unique trial was conducted in which both sedatives and intravenous opioids were able to be avoided in the regional anaesthetic group because of the nature of the surgical procedure (extracorporeal shock wave lithotripsy). Despite the absence of potent centrally acting drugs, the incidence of POCD in the regional group was not less than the group who received general anaesthesia.[44] This provided evidence that POCD does not solely result from the action of anaesthetic agents or other centrally acting drugs

WHAT IS THE CAUSE OF POCD?

If anaesthesia (including cardiopulmonary bypass) is not the cause of POCD, the question remains as to what is the cause. Surgically induced stress and inflammation

and patient susceptibility (or a combination of the two) appear to be the most likely factors. Patient susceptibility is related to the emerging understanding of baseline cognition including Alzheimer's disease (AD) which is discussed below.

Tissue injury associated with surgery is known to lead to acute inflammation at the surgical site with an influx of leukocytes producing pro-inflammatory cytokines.[45] These act as signaling molecules locally but also enter the blood stream where they can be measured in the plasma. Buvanendran and colleagues have also shown that interleukin-6 (IL-6) is also increased in the CSF.[46] It is generally agreed that inflammatory and immune mediators do not readily cross the blood brain barrier, so it is pertinent to consider how these may exert a central effect. The cytokines that have received most attention as important for immune-to-brain communication are interleukin-1 β (IL-1 β), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF- α). There are a number of possible mechanisms by which these cytokines communicate with the brain. With an intact blood brain barrier, communication can occur by circumventricular organs lacking a blood brain barrier, (easily saturated) carrier mediated mechanisms, cytokines interacting with the vagus or peripheral nerves, and stimulating cells in the blood brain barrier to produce other mediators of inflammation.[15] In addition, microglia act as central inflammatory cells and may be stimulated by neuronal input, including potent nociceptive activity.

That acute inflammation can lead to cognitive changes is well documented in the non-surgical setting. Holmes et al found that a history of an acute inflammatory event in the previous 6 months was associated with a two-fold increase in the rate of cognitive decline over 6 months; high baseline TNF- α levels were associated with a 4-fold increase in the rate of cognitive decline.[47] Importantly, the contribution of acute to chronic inflammatory conditions caused marked cognitive decline. Subjects with high baseline levels of TNF- α and an inflammatory episode over the previous 6 months had a 10-fold increased rate of cognitive decline compared to subjects with low levels of TNF- α at baseline and no inflammatory episodes. Changes in the CNS microglia and astrocytes in ageing amplify these inflammatory responses in animals and humans.[48] The fluctuations in cognitive state which characterize the progression of Alzheimer's disease, particularly the early clinical stage of Mild Cognitive Impairment (MCI), may be explained in part by the variations in blood levels of inflammatory mediators.[49]

DEMENTIA AND ANAESTHESIA

There is a distinct difference between POCD, identified by neuropsychological changes, and dementia, which severely effects cognition and impinges on daily life and behavior. Unfortunately this distinction is sometimes lost in the literature.[50] Although there is sound evidence that POCD is detectable in the elderly at seven days and 3 months after anaesthesia and surgery and is identifiable 5 years after cardiac surgery, there is no verdict at present on the association of POCD with dementia.

Apart from historical reports of a link between A&S and dementia (*vide supra*) there has been no prospective study investigating this issue. Consequently there is no high level evidence either confirming or refuting such a link. A recent meta-analysis summarized 15 case-control (retrospective) studies and found no significant association between anaesthesia and surgery and subsequent dementia (pooled OR, 1.05; 95% CI, 0.93 to 1.19).[51] The authors acknowledged the limitations of these specific studies, in addition to the general limitations of case-control studies. The sample sizes were small, the controls differed, anesthesia details were poor and there

were differing criteria for diagnosis of dementia. Most of the limitations tended to bias toward finding no association. If reviewing these studies demonstrates anything, they confirm a lack of quality research to provide high level evidence. The authors consistently call for prospective randomized controlled trials or at least prospective cohort studies, echoing the same call from the Consensus statement, First International Workshop on Anesthetics and Alzheimer's disease.[52] It is of interest that many of these studies were undertaken before there was recognition of the high prevalence of both mild cognitive impairment and dementia in the elderly. A recent publication by Chen et al which involved analyzing data from the Taiwan National Health Insurance Research Database for links between dementia and previous surgery, found an association between a surgical procedure and the development of dementia. [53] However, the limitations mentioned above still apply.

PSYCHOGERIATRICS

An important parallel is that while anesthesia and surgical studies on postoperative cognition were being undertaken in the 1980s and 1990s, psychogeriatric medicine was focusing on classifying dementia and related cognitive deficits. Gradually the importance of Alzheimer's disease (AD), (which had been previously thought as a rare disease of the middle-aged) was recognized as a common cause of dementia in the elderly, and it is now established as the most common cause, exceeding the prevalence of vascular and other causes (e.g. Lewy body and Parkinsonian dementia) although the combination "mixed dementia" is often present.

Concurrent with the widespread recognition of AD as a prominent cause of dementia, several investigators began to classify more subtle changes in cognition in the elderly. These changes were not severe enough to be classified as dementia and were identified by poor performance on neuropsychological tests either with or without subjective complaints. The classification by Petersen known as Mild Cognitive Impairment (MCI) has gained acceptance.[54] MCI is defined as:

1. Memory complaint, preferably corroborated by an informant
2. Memory impairment documented according to appropriate reference values
3. Essentially normal performance in non-memory cognitive domains
4. Generally preserved activities of daily living
5. Not demented

Loss of episodic memory is the typical finding in MCI, although other cognitive domains such as semantic memory, attention and executive function may also be affected. Petersen has classified MCI as amnesic single domain or amnesic multiple domain.[54] These requirements are consistent with the diagnostic criteria for Mild Neurocognitive Disorder in the recent DSM-5 which considers cognitive performance to have declined when it is 1-2 SD below reference values.[1] The concept of MCI is important because it is known that these individuals progress to Alzheimer's dementia at a rate of approximately 10% per year.[54]

In 2011, The National Institute on Aging (NIA) and the Alzheimer's Association (AA) classified AD into three phases based on the current understanding of the natural history of the disease[55]:

1. A preclinical phase (characterised by biomarkers)
2. Mild cognitive impairment

3. Dementia.

The biomarkers reflect the accumulation of amyloid beta in the brain, the hallmark of AD, and consist of either a characteristic CSF protein profile of amyloid beta, tau and phosphorylated-tau or the presence of amyloid using MRI/PET scan. Biomarkers thus signal the early stages of AD and are believed to occur many years before the onset of symptoms. This is not unlike the association between patterns of cholesterol subtypes and coronary artery disease. Eventually this biomarker pathology is reflected as a subtle change in cognition, phenotypically MCI. In the long term this MCI progresses to the frank dementia of AD. The whole process from preclinical disease through to dementia is a continuum taking years and even decades to progress.

THE MERGING OF TWO DISCIPLINES

Remarkably, research into POCD (anaesthesia and surgery) and AD (psychiatry, geriatrics, neurology) has occurred independently of each other. Despite the fact they address the same population they have advanced in parallel over the last twenty years. Both have utilized neuropsychological testing to identify cognitive decline. Both have used an objective decline as an essential element. In psychogeriatrics it has been a decrease of 1 or 1.5 SD compared to population norms. In anesthesia and surgery the most robust definition of decline has used a decrease of 2 SD compared to a non-operative control group. Anesthesia and surgery cognitive researchers have not placed emphasis on subjective reports[56] while psychogeriatric research and practice has found this very useful.[57] Additionally, both disciplines have repeatedly identified identical associations with cognitive decline, i.e. increasing age and lower years of education (or IQ). The overlap between MCI and POCD is thus important to clarify.

This overlap has a number of implications. Firstly, many elderly patients aged >65 y presenting for A&S will have AD in any one of the three stages. Prevalence estimates of MCI in the elderly (aged > 65 y) of 22% for elective hip replacement are consistent with population studies.[54] The prevalence of dementia in those aged >65 y is 10%.[58] Finally, the number of individuals who have AD in the preclinical stage is estimated at 31%. [59] The aggregation of AD in all the three stages approximates 63%. In other words, more than half the elderly individuals presenting for A&S may have AD pathology even though they may not have any symptoms. The prevalence may be even higher because individuals who undergo surgery generally carry more co-morbidities (increasing the risk of AD) than individuals in population studies. In 152 subjects aged 60 y or more scheduled for elective hip replacement a prevalence of amnesic MCI of 22% [95% CI, 16–29%] was found.[60] Co-morbidities in this group were diabetes (9%) hypertension (53%), smoking (current or previous) 48%, and hypercholesterolemia 35%.

Individuals who have AD can be expected to undergo cognitive decline over the ensuing years. The *key issue* is to establish whether A&S is harmless, initiates decline, accelerates the rate of decline or exacerbates a current state of decline.

This issue is further compounded by the greatly increased numbers of elderly presenting for A&S. In Australia, government databases show that in 2010 those aged ≥ 65 y constituted 13.5% of the population but received 32.2% of the anesthetics administered and projections for 2050 are that this age group will have increased to 24.2% of the population and receive 48.4% of the anesthetics. In the USA over 19 million anesthetics are administered to subjects >65 y every year.[61]

THE CASE FOR DEFINITIVE TERMINOLOGY

The preceding information has established that:

1. Elderly patients are susceptible to cognitive decline following anaesthesia and surgery
2. This cognitive decline has been termed Postoperative Cognitive Dysfunction (POCD) in the anaesthesia and surgical literature
3. POCD is identified by the administration of neuropsychological tests; it is often subjectively un-noticed; it is identifiable for at least 3 months (but even possibly 5 years); it is associated with adverse clinical outcomes
4. POCD is inconsistently defined and measured in clinical trials, in part because of a lack of formal classification or definition
5. POCD shares common factors with other geriatric cognitive conditions, especially Mild Cognitive Impairment
6. Further research can only proceed with the presence of clear definitions

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