MORE than 50 yr ago, clinicians reported changes in mental function after anesthesia and surgery in the elderly. As these phenomena have been elucidated in subsequent years, they have been categorized into the distinct syndromes of delirium and postoperative cognitive dysfunction (POCD). These phenomena seem to be increasing in prevalence, concomitant with the increase in the number of elderly patients undergoing surgery. In this brief clinical review, we describe the presentation of, course of, risk factors for, and when applicable, management of these syndromes. Delirium and cognitive function after cardiac and neurosurgical procedures are distinct subjects beyond the scope of this review.

Postoperative Delirium

Clinical Presentation and Diagnosis

Delirium was well described in the writings of Hippocrates 2,500 yr ago. The key diagnostic features, as described in the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders are (1) that it is a change in mental status, characterized by a prominent disturbance of attention and reduced clarity of awareness of the environment; and (2) that it has an acute onset, developing within hours to days, and tends to fluctuate during the course of the day. The inability to focus, sustain, and shift attention is accompanied by other cognitive symptoms (e.g., disorientation, episodic memory dysfunction) and/or perceptual disturbances (misinterpretations, illusions, or hallucinations). Associated features include disturbances of the sleep-wake cycle and activity level, as well as affective disturbance (mood lability, anger, sadness, euphoria) and thought disorder (disorganized thinking, delusions). The symptoms of delirium are numerous, vary from patient to patient, vary within patients over time, and are shared by a variety of other disorders such as dementia, anxiety, depression, and psychosis, all of which contribute to difficulties in diagnosis.

The heterogeneous presentation of delirium has led to the identification of hyperactive, hypoactive, and mixed subtypes.1,2 The hyperactive form of delirium tends to be clinically obvious. The hypoactive form, however, is often unrecognized, misdiagnosed, mistaken for depression or dementia, or simply attributed to old age, because patients may seem quiet and subdued in their disorientation. Furthermore, the relation between delirium and dementia is complex, and the syndromes may overlap.1,2

Delirium can be caused by, or associated with, a wide variety of conditions,1,2 and the current Diagnostic and Statistical Manual of Mental Disorders system differentiates subtypes based on the presumed etiology. These are delirium due to a general medical condition, substance-induced delirium (due to medication use or toxin exposure), substance intoxication delirium (due to intoxication), substance withdrawal delirium, delirium due to multiple etiologies, and delirium not otherwise specified (for cases in which there is insufficient evidence to establish a specific etiology).

Delirium in the postoperative period can be divided into emergence delirium and postoperative delirium (PD), based on the time of onset (fig. 1). Emergence delirium is seen during or immediately after emergence from general anesthesia and usually resolves within minutes or hours. It occurs in all age groups, with some predominance in children. It seems to be directly correlated with the administration of general anesthesia, because it occurs during the emergence process, mimics stage II (excitation) of ether anesthesia as described by Guedel, and usually resolves without sequelae. Emergence delirium fits the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, diagnostic criteria for a substance-induced delirium. The reader is referred to a more complete review of this subject.3

After surgery, another type of delirium occurs that is not clearly related to emergence from anesthesia. Elderly
patients commonly emerge from anesthesia smoothly and demonstrate coherence in the postanesthesia care unit. After a lucid interval, some patients develop a syndrome referred to as **interval delirium** or **postoperative delirium**. Postoperative delirium tends to first be observed between postoperative days 1 and 3, and usually resolves within hours to days, although symptoms may persist for weeks to months. Postoperative delirium is more likely to result in complete recovery than other forms of delirium. The term **intensive care unit (ICU) delirium** describes delirium that occurs in the intensive care unit, primarily in those patients requiring mechanical ventilation; it was previously referred to as **ICU psychosis**. ICU delirium makes no distinction between medical and surgical patients, so many cases of ICU delirium could also be classified as postoperative delirium.

There are a number of structured instruments available that can be used by a variety of personnel to diagnosis and assess delirium. Three validated methods include the Confusion Assessment Method, the Delirium Rating Scale Revised-98, and the Delirium Symptom Interview. The confusion assessment method has been used for most postoperative delirium research and has been modified and validated for use in critical care patients receiving mechanical ventilation.

**Incidence of and Risk Factors for PD**

The reported incidence of PD is 5–15% in older adults after general anesthesia. The reported incidence in patients undergoing surgery for hip fracture is higher, ranging from 16% to 62%, with an average rate of 35% across 12 studies of 1,823 patients. Delirium is indeed the most common complication after hip fracture, but this patient population also has a high incidence of delirium before surgery.

In elderly patients hospitalized for reasons other than surgery, the risk of developing delirium while hospitalized is predicted by an interaction between vulnerability factors present at the time of hospitalization and noxious injuries, or precipitating factors that occur during hospitalization. Among the predisposing risk factors identified are vision impairment, severe illness, cognitive impairment, and serum urea nitrogen:creatinine ratio of 18 or greater. The precipitating factors identified are use of physical restraints, malnutrition, more than three medications added 24–48 h before the onset of delirium, use of a urinary bladder catheter, and iatrogenic events, including fluid and electrolyte abnormalities and infections.

Studies in surgical patients have identified age 70 yr or older, history of delirium, history of alcohol abuse, and preoperative use of narcotic analgesics as preoperative predisposing risk factors for PD. Preoperative depression also seems to be a risk factor for postoperative delirium. Perioperative risk factors include greater intraoperative blood loss, more postoperative transfusions, postoperative hematocrit less than 30%, and severe postoperative pain. There are contradictory reports on the role of perioperative hypotension and hypoxemia in the development of PD. The role that postoperative pain plays in the development of PD is not attributable to method of analgesia, type of opioid analgesia, or cumulative opioid dose.

Drug effects are considered an important cause of delirium. In medical patients, the most important drug classes associated with delirium are the sedative–hypnotics, narcotics, and anticholinergics, all of which are routinely used in perioperative care. The role of benzodiazepines is controversial. Lorazepam has been specifically associated with the development of delirium in the ICU. There is extensive literature investigating the proposition that regional anesthesia would be associated with less delirium than general anesthesia; however, the majority of these studies show no difference.

**Pathophysiology**

The underlying pathophysiology of delirium in general, and PD specifically, remains elusive. Delirium is the behavioral manifestation of diffuse cortical dysfunction and is associated with diffuse slowing of background activity in the electroencephalogram (except in cases of alcohol withdrawal, in which there is an increase in fast wave activity). It is also associated with disturbances in a wide variety of neurotransmitter systems, and disruption of cholinergic transmission seems to be especially
important. Toxicity from anticholinergic agents mimics the electroencephalographic and behavioral aspects of delirium and is reversed by physostigmine. Serum anticholinergic activity is associated with delirium in postoperative patients. Other potential mediators include melatonin, norepinephrine, and lymphokines.

Impact of Postoperative Delirium

Postoperative delirium is associated with increased morbidity (including risk of injury), mortality, duration of hospital stay, nursing home placement, and technical (nonphysician), consultant, and nursing costs. In a recent study, duration of hospital stay for surgical patients was 6.0 days for those who developed delirium and 4.6 for those who did not. The average additional in-hospital cost per surgical patient with PD was $2,947, which equates to more than $2 billion additional health-care dollars per year in the United States.

Prevention and Treatment

It is possible to prevent PD in some patients using safe and effective interventions for systematic detection and management of predisposing factors. The most widely studied intervention program to prevent delirium in elderly medical patients is the Hospital Elder Life Program. Interventions are targeted towards six risk factors for delirium: cognitive impairment, sleep deprivation, immobility, visual impairment, hearing impairment, and dehydration. Some of the specific interventions include frequent presentation of orienting information (such as prominent display of the date, time, schedule, and names of hospital personnel), cognitive stimulation activities, physical exercise, use of visual aids and adaptations, use of auditory amplifying devices, nonpharmacologic methods to promote sleep (such as drinking warm milk before bed, relaxing music, back massage, noise-reduction strategies), and feeding and fluid assistance. Other protocols have focused on coordinated geriatric services, geriatric–psychiatric consultations, and patient and family education. A series of randomized and nonrandomized trials indicate that a substantial absolute risk reduction (in the range of 13–19%) can be achieved. A trial of proactive geriatric consultation in hip fracture patients reduced delirium by more than one-third and reduced cases of severe delirium by more than one-half.

Treatment of agitation poses a special problem. Agitation puts the patient, visiting family, and staff at risk for physical injury and interferes with administration of normal postoperative care, but current treatment options are less than optimal. Attempts should be made to avoid the use of physical restraints, which may worsen delirium and agitation. Pharmacologic therapy is used specifically to decrease agitation. Haloperidol, a typical antipsychotic dopaminergic antagonist, is administered to adults at a dose of 0.5–1 mg intravenously every 10–15 min until the agitated behavior is controlled.

Intravenous administration of haloperidol is an off-label use of the medication. Intramuscular dosing is less desirable but can be employed using 2–10 mg, waiting 60–90 min between doses. By careful dosing, practitioners should limit the degree of haloperidol’s sedative side effect, because this drug has an extended half-life in the elderly (up to 72 h) and deep sedation can last for several days. It is important for the clinician to recognize that haloperidol can be useful in the immediate management of agitation but does not alter the duration of delirium. Newer antipsychotic medications, such as ziprasidone and olanzapine, are administered intramuscularly and are reportedly effective in the management of acute agitation but have not been tested in patients with either medical or surgical comorbidities. Although most typical antipsychotics increase the corrected QT interval and may predispose to arrhythmias, haloperidol has a relatively lower propensity to do so. Cases of sudden death are rare and have not been clearly related to haloperidol.

Although it is reasonable to assume that benzodiazepines would be an effective treatment for agitation in the context of PD, anecdotal experience has shown that these medications may have a paradoxical effect in elderly patients and may worsen agitation. If alcohol withdrawal is suspected to be the underlying cause of delirium, however, benzodiazepines are the treatment of choice.

Postoperative Cognitive Dysfunction

The term postoperative cognitive dysfunction (POCD) describes a deterioration of cognition that is temporally associated with surgery. As opposed to delirium, in which pathognomonic behavior must be detected, detecting, assessing the severity of, and characterizing POCD depends on valid assessments of preoperative and postoperative cognitive function. The neuropsychological examination measures the information processing abilities of the brain through a battery of tests (assessing attention, perception, verbal abilities, learning and memory, and abstract thinking) that are sensitive to the effects of brain injury and disease.

The wide variability in normal human cognitive capacities associated with aging and a possible incidence of preexisting mild cognitive impairment in the elderly make baseline (i.e., preoperative) measures a critical component of these evaluations. In the absence of baseline data, it is impossible to associate low postoperative test scores to surgical, anesthetic, or illness variables with certainty. Subjective self-reported cognitive symptoms do not substitute for objective cognitive testing, because a poor relation between the two types of data has been demonstrated repeatedly.

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[1] Intravenous administration of haloperidol is an off-label use of the medication.
Methodologic Issues in the Study of POCD

There are a number of methodologic inconsistencies among studies that make the limited literature on POCD difficult to interpret. These include the selection of test instruments, timing of postoperative testing, inclusion and exclusion criteria, the inherent variability of cognitive testing, and most fundamentally, the operational definition of POCD.

Test Selection. Mental status screening instruments such as the Mini-Mental State Examination are useful for detecting frank dementia but lack the sensitivity and specificity required to detect milder or more selective forms of cognitive impairment. High-functioning patients who have experienced a mild decline in cognitive function and patients with "focal," as opposed to "diffuse," cognitive dysfunction may achieve high Mini-Mental State Examination scores. Cognition is not a unitary process, but rather is the result of activity in multiple complex, distributed, and interacting neuronal circuits that underlie specific information processing functions. There is no single measure of cognitive status; therefore, comprehensive neuropsychological assessment requires that a battery of tests assessing a variety of cognitive domains must be used. There are, however, a wide variety of tests available, which differ in their test–retest reliability, sensitivity, specificity, and the degree to which they are subject to practice effects.

Timing of Postoperative Testing. Another methodologic inconsistency among the studies is the timing of postoperative cognitive testing. In general, studies measuring cognitive function shortly after surgery find a much higher incidence of POCD than studies measuring cognitive function weeks to months after surgery. Longitudinal studies have the problem of attrition, which does not occur randomly but is influenced by the postoperative health status, functional status, and possibly the cognitive status of the patient. Patients who develop POCD may be more likely to drop out of the study, thus underestimating the true incidence of POCD.

Inclusion and Exclusion Criteria. It is also important to consider the subject inclusion and exclusion criteria when interpreting study findings. Recently, the term mild cognitive impairment has come to represent a transitional zone in the spectrum of cognitive function from normal aging to progressive dementing conditions, such as Alzheimer and cerebrovascular diseases. Unfortunately, patients with preoperative mild cognitive impairment have not been differentiated in studies of POCD. Therefore, there is no information available concerning the impact of surgery and anesthesia on this subset of patients that may be at greatest risk for POCD. There is no evidence that anesthesia and surgery increase the incidence of Alzheimer disease.

Operational Definition of POCD. One of the greatest problems facing the investigation of postoperative cognitive function is the absence of a consensus regarding the operational definition of POCD. Variations in the methods that different groups have used to define deterioration in cognitive function in part underlie the difficulty in comparing studies. Furthermore, few studies use control groups and take practice effects into account.

The percent change method involves converting the preoperative to postoperative difference score into a percent of baseline score, i.e., (postoperative score - preoperative score)/preoperative score. This method generates continuous data, which can then be averaged across patients for group comparisons. The use of group mean analyses, however, is discouraged, because a subset of subjects experiencing significant deterioration may be masked when other subjects exhibit improved performance over time. The SD method involves identifying patients who experience a postoperative decline of some criterion number of SD units (Z-scores). The International Study of Postoperative Cognitive Dysfunction (ISPOCD) studies (see below) required a 2-SD decline to qualify as POCD. Limitations of the SD method include the following: (1) in patients with low baseline scores, it may not be possible to decline by more than 1 SD (i.e., floor effect); and (2) the absolute magnitude of change in raw test scores required to meet the criterion differs between studies, because they are derived from the preoperative test scores of the baseline sample. A third strategy involves identifying patients who experience a specific percentage (e.g., 20%) decline from baseline of at least a specific percentage (e.g., 20%) of the tests administered. A limitation of this technique is that patients with lower preoperative test scores require a smaller decline in raw score to meet the 20% criterion. It should be noted that the methodology used by ISPOCD is a subset of the general assessment technique referred to as a reliable change index. Lewis has recently explored a number of issues related to the use of this technique.

Incidence of POCD

In 1998, Möller et al.27 presented the first of a series of multicenter studies from the ISPOCD that primarily included European centers. Information from the ISPOCD studies is available at the ISPOCD Web site. The ISPOCD1 study tested the hypothesis that insufficient oxygen delivery to the brain, as assessed by the presence of hypotension and/or hypoxemia, is a causative factor for POCD. The study included 1,218 patients, aged 60 yr or older, who underwent major abdominal, noncardiac thoracic, or orthopedic surgery during general anesthesia. Patients were tested preoperatively and at 1 week and 3 months postoperatively. Test results were compared with a total of 321 controls recruited from the United Kingdom, 11 centers in Europe, and 2 centers in North
America. Patients were classified as experiencing cognitive dysfunction when two Z scores in individual tests declined by 1.96, or the combined average Z score declined greater than 1.96. At 1 week postoperatively, 25.8% of 1,011 patients experienced a decline in cognitive function, compared with 3.4% of 176 control subjects. At 3 months postoperatively, 9.9% of 910 patients experienced a decline relative to preoperative level of function, compared with 2.8% of controls.

A number of subsequent studies have described cognitive impairment within the first 10 days after surgery and anesthesia. Williams-Russo et al. found a rate of POCD of 5% at 6 months after surgery, although in the absence of a control population, the significance is hard to determine. A follow-up study that evaluated patients at 1 and 2 yr found that the rate of POCD decreased to approximately 1%, which was not statistically significant. Taken together, it seems that elderly patients manifest measurable deterioration shortly after surgery and anesthesia (25% at 2–10 days), with gradual resolution such that the incidence declines (10% at 3 months, 5% at 6 months, 1% at 1 yr) to levels nearly indistinguishable from control subjects by approximately 1 yr. Two important limitations are that (1) given the tendency of impaired patients to drop out of such studies, the long-term follow-up may underestimate the true incidence of deterioration; and (2) the clinical course of an individual patient cannot be clearly inferred from this understanding, in that there is inconsistency between the testing sessions. In the ISPOCD studies, less than half of the participants who were classified at having POCD at 1 week was significantly associated with increased age, increased duration of anesthesia, fewer years of education, second operations, postoperative infections, and respiratory complications. Only age was a significant risk factor for POCD at 3 months.

Acute postoperative pain has also been associated with poorer postoperative cognitive function. In a study of 24 patients aged 61–86 years who underwent elective lumbar spine surgery, greater pain on postoperative day 1 was associated with poorer performance on some neuropsychological tests. The degree of chronic preoperative pain was not related to preoperative cognitive test performance.

**Etiology of POCD**

To date, the etiology of POCD remains unclear. Cerebrovascular disease, cerebral hypoperfusion, genetic susceptibility, alteration in neurotransmitter function, neurohumoral stress, and central nervous system (CNS) inflammatory phenomenon have all been suggested, but the principal suspect has been general anesthesia. General anesthesia is a state achieved with multiple medications, many of which are purported to cause delirium. The preferred method of evaluating the potential of general anesthesia to produce POCD has been randomized trials of general versus regional anesthesia. Numerous studies suggest that choice of anesthesia is not an important factor in the development of POCD. This issue is discussed in greater detail below. Although such radically different anesthetic techniques as regional and general anesthesia have similar impact on postoperative cognitive function in clinical studies, there are laboratory studies suggesting that general anesthetic agents have toxic effects on CNS structure and function. The relevance of this work to the clinical syndromes described will require significant additional research.

Hypoxemia and ischemia are potential etiologies of POCD for which potential treatments exist (e.g., supplemental oxygen), that were initially evaluated in the 1940s. The first ISPOCD study examined the role of hypotension and hypoxemia as potential etiologies. Oxygen saturation was measured by continuous digital pulse oximetry, and blood pressure was measured by intermittent noninvasive oscillometry throughout the perioperative period. Despite high rates of profound hypoxemia and hypotension, neither condition was associated with POCD. Cerebral oximetry may provide...
additional insight into this problem. Further research is necessary to clarify the role of cerebral ischemia in the etiology of POCD.

The ε4 allele of the ApOE gene is strongly associated with the development of Alzheimer disease but has not been found to be an important predictor of POCD in general surgery. The search for either a genetic predisposition to POCD or a biomarker of POCD is intriguing, but all such efforts remain highly theoretical. In small studies of cardiac surgery patients, nonspecific enolase, but not S100β, may be useful as a marker of early POCD. Current research interests, including small nucleotide polymorphisms that code for different aspects of inflammation (in cardiac surgery) and stable nitric oxide end products, will require substantial additional research to establish clinical utility.

**Regional versus General Anesthesia**

It is intuitively appealing that general anesthesia, which specifically affects the brain, as compared with regional anesthesia, which affects primarily the spinal cord or peripheral nerves, would be associated with different rates of POCD. Beginning in 1980, a series of relatively small studies suggested that patients undergoing general anesthesia, but not neuraxial anesthesia, were at greater risk for POCD. In 1995, Williams-Russo et al. presented an adequately powered, prospective, randomized study of POCD that used standard neuropsychological instruments. This study compared the effect of epidural versus general anesthesia on the incidence of POCD in patients undergoing elective unilateral total knee replacement. Neurocognitive assessment was performed 1–7 days preoperatively (n = 262) and 1 week and 6 months (n = 251) postoperatively. Group mean scores for each of the 10 measures were compared between the two anesthesia groups, but no statistically significant differences were observed postoperatively. In addition, the proportions of patients exhibiting clinically important decrements for each test (defined by consensus) were compared. Overall, 5% of patients exhibited a decline in cognitive function 6 months after surgery, but no statistically significant differences were found between the anesthesia groups. As this was a comparative trial, there was no control group for reference. Recently, Wu et al. provided a comprehensive review of 24 studies that evaluated the choice of anesthesia and concluded that it does not influence the incidence of POCD.

**Relation between Delirium and Cognitive Dysfunction**

Despite the distinguishing characteristics of PD and POCD, it is important to consider that there may be an association between them. Postoperative delirium may be a harbinger of POCD or an emerging dementia. Patients who developed delirium in the ISPOCD1 study were not the same patients who developed POCD. In ICU patients, delirium does seem to be prodrome of long term cognitive impairment. The majority of studies to date have focused on either PD or POCD. In the near future, studies that undertake sophisticated evaluations for both PD and POCD should shed further light on this issue.

**Conclusions**

Central nervous system dysfunction after anesthesia and surgery is primarily a problem of the elderly. The combination of an aging population and improvements in both anesthesia and surgery has led to increases in the number of elderly patients undergoing surgery. It is highly likely, therefore, that postoperative CNS dysfunction will become an increasingly common problem. Postoperative delirium is an established diagnostic entity that requires further research to understand its etiology as well as to formulate effective preventive and treatment strategies. There are regimens available that seem to diminish postoperative delirium. Implementation of these regimens may be difficult given limited resources; however, assessment of patients for delirium has become a standard of care in some European and American hospitals. Perioperative physicians should be familiar with the prevention, diagnosis, and management of PD.

In contrast to PD, the authors believe that attempts to define the presence or absence of “syndromal” POCD are premature. The experts are not yet certain regarding the exact composition of cognitive deficits that are associated with POCD, nor do they agree regarding the degree of dysfunction that is clinically significant. Any illness requiring hospitalization may be associated with cognitive decline, raising the possibility that cognitive decline occurs as a consequence of generalized illness rather than it being causatively related to surgery and/or anesthesia. There definitely are patients who manifest persistent significant impairments after surgery and anesthesia. Further study, particularly of clinical cohorts with mild cognitive impairment preoperatively, will be necessary for practitioners to understand the relative risks of cognitive dysfunction after noncardiac surgery.

Postoperative CNS dysfunction is a public health problem worthy of further study to elucidate the risk factors, preventative and therapeutic strategies, and underlying pathophysiology. Practitioners should understand the current status of postoperative delirium and cognitive dysfunction and exercise vigilance to prevent and diagnose delirium as future studies seek to understand postoperative CNS function.
References