The Risk of Going Under

Research paints a complex picture of how surgery and anesthesia might harm the brain, particularly in the elderly

By Andrea Anderson

William Sieber was working in his garden. Wasn't he? He was sure he had been picking tomatoes just moments ago. Now he appeared to be in some kind of rehabilitation hospital. And weren't people looking at him a little strangely? What on earth were they up to?

Sieber, a then 88-year-old retired pediatric surgeon, knew that something was not right. As he told his son, Fritz, a few months later, he was unable to shake the frightening fog of confusion and paranoia that enveloped him.

This delirium lasted about a week. It had started after a fairly routine spinal surgery to relieve nerve pressure caused by stenosis, the narrowing of space around the spinal cord. The 45-minute procedure went according to plan. His anesthesiologist had sedated him using a typical cocktail of drugs.

Before the operation, Sieber had not experienced any noticeable cognitive difficulties. He was living independently with his wife in a retirement community near Pittsburgh, still drove his own car and read a book a week on his favorite topics, history and gardening. But his experience in recovery "scared the daylights out of him," Fritz recalled. "He knew that he was acting, in his words, 'crazy.' He couldn't do anything about it, and that's what bothered him."

It bothered his son, too. As director of anesthesiology at the Johns Hopkins Bayview Medical Center, Fritz took a professional interest. Not long after his father's 2007 surgery, he joined the ranks of researchers studying the impact of surgery and anesthesia on the brains of elderly patients. For decades physicians have anecdotally reported mental changes, from short-term disorientation to outright dementia, in older patients following surgery. Only more recently, though, have they begun to seriously investigate the prevalence of these changes, their duration, and an array of potential causes, mechanisms and possible solutions.

So far these efforts have not turned up any definitive proof that anesthesia or surgery, or both, is directly responsible for postsurgical cognitive problems. But the circumstantial evidence is building. Several questions loom large: If the connection is real, is the main culprit consciousness-zapping drugs, the stress of surgery or the brain inflammation that can accompany it? Are specific types of anesthesia more harmful than others? Are certain patients more susceptible to surgery-related cognitive decline? And perhaps most critical, are there ways to ward off any potential negative effects?

To date, a few guideposts have emerged—among them, the importance of offering counseling and evaluating patients' cognition before they get wheeled into the operating room—but definitive answers cannot come soon enough. Every year more than 17 million seniors in the U.S. undergo surgery. With more than 75 million baby boomers hitting their golden years, the number of Americans facing hip replacements, heart repairs and all manner of other procedures is sure to rise. Soon many more seniors and their families will face tough decisions as they try to balance the best treatment options against potential risks to their cognition and quality of life.

From Delirium to Dementia?

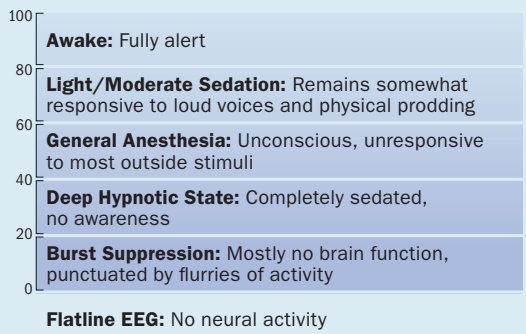
Researchers began exploring the potential cognitive effects of surgery and anesthesia in earnest in the 1990s, focusing largely on two outcomes: postoperative delirium, marked by temporary disorientation, hallucinations and memory problems, and postoperative cognitive dysfunction. The latter, known as POCD, encompasses a range of lasting deficits, among them problems with learning, memory, attention and abstract thinking. These studies suggested that postoperative delirium is remarkably common, occurring in up to half of patients older than 65, with even more patients displaying some milder confusion. They also found that POCD affected at least a third of elderly patients, although it has proved trickier to pinpoint because there is no standard way to measure or diagnose it.

In 2001 a pivotal study in the *New England Journal of Medicine* documented even higher rates of delirium and POCD—and an apparent overlap between the two. A Duke University–led team measured neurocognitive function in 261 patients, all older than 50, both before and after coronary artery bypass graft surgery. Among the tests they ran were some that measured how well these individuals remembered details from a story and a series of digits and shapes, as well as their speed at drawing lines through sequential numbers or letters.

At discharge, typically a week after surgery, more than half of the participants showed at least a 20 percent drop in at least one of the cognitive areas tested. Many improved quickly. After six weeks, 36 percent still struggled; after six months, less than a quarter did. But for a significant number of these subjects, their cognitive problems persisted or reappeared: Five years after surgery, 42 percent of the 172 patients who returned for testing exhibited signs of cognitive decline. In patients with cognitive decline at discharge, these losses were two to three times those seen among nearly 6,000 Medicare patients tracked for five years in a separate study.

Levels of Consciousness

The bispectral index (*below*)—a value based on the brain's electrical activity, measured with electrodes on the scalp (*left*)—helps doctors to monitor how deeply sedated patients are during surgery.



FAST FACTS

STAYING SHARP AFTER SURGERY

1. For decades physicians have anecdotally reported mental changes, from short-term disorientation to outright dementia, in older patients following surgery.
2. Recently scientists have started to investigate an array of potential causes for these changes—including anesthesia, the stress of surgery and brain inflammation.
3. Some evidence links the depth of sedation to the risks for postoperative cognitive problems, but other studies suggest that deep sedation may shield the brain from trauma.
4. A few guideposts have emerged: among them, it is critical to assess a patient's cognition before surgery and to make sure he or she understands the risks.

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In the years since, a growing body of research has shown that seemingly temporary postoperative deficits can resurface months, even years, after surgery. "We do know that patients having procedures in hospital have a very high rate of delirium, and we know that that puts patients at increased risk of cognitive decline down the track," says Lisbeth Evered, an anesthesia researcher at St. Vincent's Hospital Melbourne in Australia.

Last year investigators at Beth Israel Deaconess Medical Center and elsewhere sought to quantify that risk. They tracked 560 individuals, all older than 70 and initially shown to be dementia free, undergoing total hip replacement or another major surgery. They found that 134, or about 24 percent, experienced postoperative delirium. Compared with the participants who did not have delirium, those who did were significantly more likely to show mental deterioration years down the line. Although both groups on average experienced some cognitive decline, the rate was nearly three times faster in the group who had suffered from delirium. What is not clear, however, is if the decline is caused by the delirium, or if the delirium is indicative of some underlying brain vulnerability, or if something else entirely is to blame.

Dose vs. Depth

Several months after Sieber's back surgery, he faced a knee operation. His spell of postoperative confusion had completely dissipated, but he still felt apprehensive. "I just can't have that happen to me again," he told his son. So Fritz asked his father's anesthesiologist to consider using a regional anesthetic, which can produce lighter sedation and might, he reasoned, have less of an effect on his father's thinking. She agreed, and the strategy paid off (although it is not always an option for longer surgeries). Sieber experienced no delirium and went home from the hospital after only two days, "clear as a bell," Fritz remembers. "It really got me thinking about whether there are issues with drug dosing in the elderly."

To try to find out, in 2010 Fritz and his colleagues evaluated delirium in 114 otherwise healthy elderly patients undergoing surgery for hip fractures. Instead of general anesthesia, the doctors administered varying doses of propofol via the spine. To estimate how deeply the patients went under, the researchers used a so-called bispectral index (BIS) monitor. The device gauges levels of consciousness based on the brain's electrical activity, measured with electrodes placed on the scalp. They found that after surgery, the patients who had been only lightly sedated as measured via BIS—regardless of how much anesthesia they received—experienced half the rate of postoperative delirium compared with the rest. In other words, sedation depth and not anesthetic dose had predicted whether or not someone experienced delirium.

Other studies, however, do link anesthesia dose to delirium. In 2013 researchers at the Chinese University of Hong Kong evaluated 921 elderly patients undergoing major surgery, only some of whom received BIS monitoring to make sure they stayed minimally sedated. Compared with the group that was not monitored, BIS-monitored patients received, on average, 21 percent less propofol when it was administered intravenously and 30 percent less via inhalation. They were also more than 30 percent less likely to have postoperative delirium or to have POCD three months after discharge. The lower exposure to anesthesia may have been the "crucial factor," says Duke anesthesiologist Miles Berger, who was not involved in the work.

Complicating this picture, though, additional evidence hints that deep sedation may sometimes protect patients' brain function. In 2015 Mount Sinai Hospital anesthesiology, geriatrics and palliative medicine researcher Stacie Deiner and her colleagues reanalyzed BIS measurements from 105 older individuals undergoing major surgery with intravenous or inhaled general anesthesia. They found that patients who spent 50 percent more time in deep anesthetic states had lower POCD rates, on average, three months after surgery. Those who were deeply sedated for longer also displayed more burst suppression, a type of neural activity characterized by almost no brain function, punctuated by flurries of activity. Deiner's team suspects that sustained periods of burst suppression, brought on by deep sedation, may shield the brain from trauma.

Her study highlights a central question about whether anesthetics harm or protect the brain. This uncertainty persists, in large part, because researchers still do not fully understand how anesthetics work. In general, these drugs slow nerve firing throughout the brain. But as Imperial College London biophysics and anesthetics researcher Nick Franks explains, some also boost neural activity along the pathways that make us sleepy. On another level, research suggests that anesthetics disrupt the way in which neurotransmitters typically interact with their receptors. Many common anesthetics, including sevoflurane and propofol, bind to receptors that regulate memory, attention and concentration and may even rewire connections essential to these functions, according to researcher Laszlo Vutskits of the University of Geneva.

Up to half of older patients suffer from delirium after major surgery. Perhaps a third have postoperative cognitive dysfunction, which may resolve, persist or vanish and then resurface.

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Animal studies consistently show that some general anesthetics injure neurons, alter the branchlike dendrites that allow nerve cells to communicate and trigger learning problems. But they also show that other drugs may safeguard the brain from damage. It may be that an animal's age helps to determine the permanence of any neuronal changes. Vutskits argues, for instance, that young, developing brains are flexible enough to compensate for or reverse anesthesia-induced modifications [*see box below*]. The likelihood that postoperative cognitive problems stem from more than one factor is "one of the things that makes understanding human models so confusing," Deiner says.

The Link to Inflammation

Sieber recovered quickly from his second surgery but started to show signs of dementia a few years later. His mental capacity continued to deteriorate until his death in 2015. Sieber's trajectory—cognitive difficulties that emerge after surgery, then dissipate and ultimately return—matches that of many patients. Given the slew of unanswered questions concerning anesthesia, his son, like many other experts, began to consider factors such as surgery itself and a presumed consequence: neuroinflammation.

Inflammation is our body's natural response to a trauma—immune cells release chemicals to help heal damage, keep intruders at bay and protect us from further harm. But sometimes this defense mechanism goes awry, launching a full-fledged war when only a small surge is warranted. Many investigators now believe that surgery can trigger brain inflammation, which in turn produces cognitive problems. "You get an inflammatory insult as a result of the surgery that is then redirected at the brain," says anesthesia researcher Roderic Eckenhoff of the University of Pennsylvania.

A series of studies have shown that rodents display robust inflammatory responses to surgery, which increase their risk of POCD-related brain damage. In 2016 one mouse study found that surgery triggered inflammation in the brain's memory center, which impaired the animals' powers to recall a familiar mouse, among other tests. In contrast, when the animals received just anesthesia, without surgery, they showed no memory problems. The same study reported that mice that were engineered to lack a normal inflammatory response or that received an anti-inflammatory drug during surgery could also sidestep these cognitive costs.

Unfortunately, the findings are less straightforward in humans. If, for instance, neuroinflammation leads to cognitive issues, then brief, relatively noninvasive surgeries should probably be less risky. But in a 2015 pilot study, chief of geriatrics Cynthia X. Pan and her colleagues at NewYork-Presbyterian/Queens Hospital compared mental outcomes in dozens of older individuals undergoing either laparoscopic colon surgery, involving small incisions, or more invasive colon surgery. They found that almost half of all patients experienced POCD, and its occurrence in both groups was essentially the same. Also confounding was a Chinese study in which investigators ran-

What about the Risks for Kids?

GETTY IMAGES

Do children who need surgery face the same cognitive risks as older patients? Some epidemiological studies suggest that early exposure to surgery and anesthesia might lead to neurodevelopmental problems down the road, but the most robust research tends to show no long-term cognitive consequences.

In 2016 Andrew Davidson, an anesthesia and pain management researcher affiliated with the Murdoch Childrens Research Institute and Royal Children's Hospital Melbourne in Australia, and his colleagues looked at cognitive outcomes in more than 700 children who had inguinal hernia surgery as infants. The babies randomly received spinal or general anesthetic for just under an hour. When the researchers reassessed the tots a year or so later, both groups performed equally well on tests of cognition, language, motor skills, behavior, and social or emotional skills. "At the age of two, there's no difference whatsoever," Davidson says. "That doesn't mean that there isn't some impact in some other neurocognitive domain," he adds, noting that the children will be assessed again when they are older.

In another study published last year, Lena Sun, a pediatric anesthesiology researcher at Columbia University, and her co-workers tracked down 105 children who had elective hernia surgery before their third birthday and received a general anesthetic for a median of 80 minutes. Five to 12 years later the investigators compared these children with their unexposed siblings in terms of IQ, memory, attention, learning, motor function and language. Again, cognitive scores were similar in both groups.

Sun says this study should be "very reassuring to parents with healthy children having brief procedures." Children needing multiple or lengthy procedures, however, may experience more lasting neural changes. Indeed, the FDA recently issued a safety warning that prolonged or frequent use of general anesthesia in very young children could harm their brain. Sun says that in such cases, "we cannot make a blanket statement that there are no problems," but current research is tackling the potential risks. —*A.A.*

The stress of surgery or resulting inflammation may play a role in cognitive decline. Another possibility: those most affected are already slipping, and surgery pushes them over the edge.

domly assigned elderly knee surgery patients to receive either paracoxib, an anti-inflammatory drug, or saline with general anesthesia. They found that the paracoxib group exhibited fewer inflammatory markers and half the rate of POCD one week after surgery. Three months out, that gap closed, casting doubt on how much inflammation harms cognition in the long run.

Other research implicates ailments such as chronic heart disease, hypertension and Alzheimer's disease, which is associated with neuroinflammation. In people with these conditions, who are already more susceptible to cognitive decline, triggering additional inflammation with surgery or drugs may hasten an ongoing process. In 2013 Eckenhoff and his colleagues at the University of Pennsylvania explored this idea, studying the effects of surgery and anesthesia on normal mice versus mice genetically engineered to develop Alzheimer's-like dementia. They found that surgery led to dramatic learning and memory problems in the genetically altered mice. But surgery in the normal mice and anesthesia in both groups had no significant impact on cognition.

Last year Katie J. Schenning and her colleagues at Oregon Health & Science University retrospectively analyzed data from two studies and compared 182 elderly individuals who had one or more surgeries under general anesthesia with 345 of their peers who had never had surgery or had at least avoided general anesthesia. They found that the group who received general anesthesia displayed significantly worse cognitive abilities over the course of seven years, on average, and showed brain shrinkage and ventricular enlargement—an expanding of brain cavities that is associated with dementia. These changes were most pronounced among surgical patients who carried the *APOE4* allele, a gene variant that increases the risk of developing Alzheimer's.

"Perhaps the people most affected are already at risk for having this cognitive decline and perhaps are already declining," says Schenning, an anesthesiology and perioperative medicine researcher. "Maybe it's gone unrecognized until they have a major life stress, such as surgery, that sort of pushes them over the cliff."

Reducing Your Risk

Did Sieber's surgeries ultimately contribute to his dementia? His son cannot rule out the possibility that his father was always at risk and would have deteriorated anyway. "Part of the issue with older adults is that what you're observing is part of a longer trajectory of decline," Deiner says. "So understanding whether the person is having just normal age-related changes versus having an actual problem related to surgery and anesthesia can be a bit thorny to figure out."

Whatever the cause, cognitive problems postsurgery present serious challenges to patients and their families. Esther Oh, co-director of the Johns Hopkins Memory and Alzheimer's Treatment Center, describes one all-too-common scenario: an elderly person has routine surgery and winds up either dependent on family members or needing an assisted living facility. Before that happens, experts are recommending several strategies that may help reduce the risk of postsurgical delirium and POCD.

First, elderly patients and their families should be advised of possible risks in a frank manner and be made aware of any nonsurgical options. For those facing surgery, Sieber advocates preoperative screening for subtle cognitive impairment. Those who show signs of cognitive change would benefit from adhering to evidence-based guidelines, such as Enhanced Recovery after Surgery, which aim to decrease surgical complications through counseling, to reduce physiological stress and to standardize anesthetic protocols, such as using lower doses or less sedation. Even simple tactics—such as making sure older patients always have their glasses or hearing aids at their bedside—can help reduce disorientation. Similarly, patients may feel less disconcerted if they are allowed to wake up on their own in recovery rather than being roused.

Investigators emphasize that the possible links among surgery, anesthesia, POCD and dementia should not scare anyone away from procedures that can improve health or quality of life. Instead they want to maximize patient outcomes. It is not acceptable to say, "Grandma was never quite right" after surgery, says Beverley Orser, an anesthesia researcher at the University of Toronto: "Survival's not good enough—we want them to thrive." M

MORE TO EXPLORE

- **Longitudinal Assessment of Neurocognitive Function after Coronary-Artery Bypass Surgery.** Mark F. Newman et al. in *New England Journal of Medicine,* Vol. 344, No. 6, pages 395–402; February 8, 2001.
- **Can Intraoperative Processed EEG Predict Postoperative Cognitive Dysfunction in the Elderly?** Stacie Deiner et al. in *Clinical Therapeutics,* Vol. 37, No. 12, pages 2700–2705; December 1, 2015.
- **Surgery Is Associated with Ventricular Enlargement as Well as Cognitive and Functional Decline.** Katie J. Schenning et al. in *Alzheimer's & Dementia,* Vol. 12, No. 5, pages 590–597; May 2016.

From Our Archives

- **Hidden Dangers of Going Under.** Carina Storrs; The Science of Health, *Scientific American,* April 2014.