



THE POST-OP BRAIN

Surgery can cure—but it may take a toll on cognition. Some scientists blame a body-wide inflammatory response

By Mitch Leslie

Colin Wahl, a market research consultant in Chapel Hill, North Carolina, was recovering nicely from triple bypass surgery last year when he noticed a white spot on the incision. It proved to be an obstinate infection that required three further surgeries to eradicate. Wahl, now 61, says his mind hasn't been as sharp since. "It's little things mostly related to memory." An avid recreational hockey player, he would forget to bring his skates or sticks to the rink. Certain words became elusive. Just hours after talking to a colleague about Tasmania, he couldn't recall the word. Instead, he says, the phrase "Outback Australia" was

stuck in his mind. "I'm trying to remember something and something else slips into that memory slot."

Many of us can recount a similar story about a friend, colleague, or loved one—usually elderly—whose mental condition deteriorated after a visit to an operating room. "The comment that 'So-and-so has never been the same after the operation' is pervasive," says anesthesiologist Roderic Eckenhoff of the University of Pennsylvania.

Often, surgical patients are beset by post-operative delirium—delusions, confusion, and hallucinations—but that usually fades quickly. Other people develop what has been dubbed postoperative cognitive dysfunction

(POCD), suffering problems with memory, attention, and concentration that can last months or even a lifetime. POCD not only disrupts patients' lives, but may also augur worse to come. According to a 2008 study, people who have POCD 3 months after they leave the hospital are nearly twice as likely to die within a year as are surgical patients who report no mental setbacks. With the ballooning senior population needing more surgeries, "this is going to become an epidemic," says anesthesiologist Mervyn Maze of the University of California, San Francisco.

What causes POCD, what makes some patients susceptible, and how best to protect their faculties are unclear. And some



Tim Hasledon takes a postoperative cognition test in an Ontario, Canada, hospital as part of a study to compare mental status before and after a surgery.

scientists still question whether surgery is to blame. Two prominent anesthesiologists called the idea that operations cause persistent mental declines a fallacy.

Yet more researchers and doctors are awakening to surgery's risks for the brain. Last year, the American Society of Anesthesiologists launched a Brain Health Initiative to spur research into the factors that make people vulnerable and to pinpoint preventive measures. Scientists now have a prime suspect for the cause of POCD: inflammation of the brain. And clinical trials are testing interventions that include drugs, changes in operating room procedures, and mental training. "I believe we are on the verge of some diagnostic and therapeutic advances," says Joseph Mathew, a cardiothoracic anesthesiologist at Duke University Medical Center in Durham, North Carolina.

IN THE EARLY YEARS OF SURGERY with general anesthetics, more than 150 years ago, patients were thrilled just to survive an operation, says anesthesiologist Miles Berger, also of Duke. As surgical techniques improved

and expectations rose, however, the mental state of the survivors became a concern. In 1955, an influential paper in *The Lancet* described six elderly patients whose faculties appeared to dwindle after operations.

Some studies since have suggested that such impairments are disturbingly common. For example, a 2001 paper in *The New England Journal of Medicine* tracked the consequences of coronary artery bypass surgery, which replumbs clogged heart vessels. In one form of the procedure, a heart-lung machine circulates and oxygenates the blood. Afterward, many patients complain of a mental haziness, which sometimes lasts for the rest of their lives. More than half of patients leave the hospital with signs of that "pumphead," the authors of the 2001 paper reported, and 42% are still impaired 5 years later.

Critics questioned the data because the study lacked a comparison group of patients with heart disease who didn't undergo surgery. But those scary figures made an impact in operating rooms. Worried that the heart-lung machine caused impaired thinking, many surgeons switched to a form of bypass that doesn't require the machine. As later studies revealed, however, the odds of developing cognitive difficulties are no better for that "off pump" surgery.

Still, are that many patients struggling mentally after surgery? Pinning down the incidence of POCD is difficult because we don't have standard diagnostic criteria, says cardiothoracic anesthesiologist Charles Brown IV of the Johns Hopkins University School of Medicine in Baltimore, Maryland. Depending on the definition, the "incidence can be vastly different, from 5% to 50%," he says.

The type of operation also has an effect—cognitive problems are usually more common in heart surgery patients. Further complicating the picture, patients may become sharper after certain operations, such as bariatric surgery for obesity. Clinical neuropsychologist John Gunstad of Kent State University in Ohio and colleagues found that a mental upswing occurred quickly after that surgery. By 12 weeks after their operations, people were already performing better on cognitive tests, "and that continued out to 3 to 4 years," he says.

The studies that could provide the strongest evidence for a link between surgery and mental decline—ones using control groups—are hard to do for ethical reasons, Berger says: "You typically can't randomize people either to have or not have surgery." Instead, researchers have relied on weaker evidence, often gleaned by comparing patients with different surgical histories.

Those studies have disagreed. In work published this year, anesthesiologist Juraj Sprung of the Mayo Clinic in Rochester, Min-

nesota, and colleagues measured the prevalence of mild cognitive impairment (MCI), a mental downturn that often precedes Alzheimer's disease, in more than 1700 elderly Minnesota residents. The team compared the incidence of MCI in people who had undergone an operation or procedure that required general anesthetic since the age of 40 with the incidence in people who had not. "We did not find convincing evidence" of a link between being put under and MCI, Sprung says.

Yet anesthesiologist Katie Schenning of the Oregon Health & Science University in Portland and colleagues reached the opposite conclusion last year when they analyzed data on a similar group of more than 500 elderly patients, mostly from Oregon. "People who had surgery and anesthetic declined more rapidly," she says.

Most controversial was a Danish team's study of 8500 identical and fraternal twins from a national registry in Denmark. The researchers had access to medical records for the mostly elderly twins and the results of cognitive assessments. To start, the researchers sorted the subjects into two groups depending on whether they'd had surgery in the 18 to 24 years before they took the cognitive tests. Overall, the surgery group registered slightly lower scores. Then, the researchers focused on individual pairs of twins in which only one twin had undergone surgery. The results were pretty much a toss-up, the team reported in *Anesthesiology* last year: Forty-nine percent of the time, the twin who had been operated on scored below their sibling.

In an accompanying editorial, anesthesiologists Michael Avidan and Alex Evers of Washington University in Saint Louis in Missouri argued that those results illustrated "the fallacy of persistent postoperative decline." The editorial irked other scientists who study POCD.

"Fallacy is a bit strong of a term for something we don't understand yet. I took offense to that," says Eckenhoff, who co-wrote a response published in a later issue of *Anesthesiology*. Berger notes that the first part of the study did uncover a significant effect from surgery. Even if it was small, any mental slippage might make a difference to older folks who are, say, struggling to make sense of their bank statement.

Such studies have to contend with a major confounding factor: Patients who need operations often have serious illnesses, such as cardiovascular disease, that take their own toll on the brain. Patients' intellectual powers may have started waning before they were wheeled into the operating room. "The biggest question is whether surgery and anesthesia are causing an accelerated [cognitive] decline or whether these patients would have had this decline anyway," Eckenhoff says.

To isolate the effect of preexisting illness, anesthesiologist Stephen Choi of the Sunnybrook Health Sciences Centre in Toronto, Canada, and colleagues have started to track memory and other cognitive skills in people scheduled for knee or hip replacements. The patients will take computer-based cognitive tests before and after surgery to gauge whether their faculties decline. The researchers will also try to link any changes to existing conditions, including MCI, atherosclerosis, and blood clots in the lungs.

BEYOND THE DEBATE about whether long-term POCD is real is the question of just how surgery might affect the brain. Maze admits that he was a little cocky when he started looking into the issue more than 20 years ago. “I thought, ‘Ah, simple,’” he

duced blood flow to the brain during surgery. But many scientists are now converging on the idea that POCD results from the physical trauma of surgery itself.

“The only thing worse than general anesthetic is surgery,” Crosby says. “There’s nothing bigger that will happen to most people.” In essence, he says, patients are put into a coma and assaulted. Other organs, such as the kidneys, often display impaired function after operations, Berger notes. “It’s inconceivable to me that anesthesia and surgery could be associated with damage to every organ system except the brain.”

Researchers hypothesize that surgery unleashes a body-wide inflammation, which then infiltrates the brain, particularly in the elderly. As Crosby and a colleague put it in an editorial, “Surgery sets the old brain on fire.”

Annals of Neurology, also implicates brain inflammation. Anesthesiologist Lars Eriksson of the Karolinska Institute and University Hospital in Stockholm and colleagues performed positron emission tomography scans on eight men in their 50s and 60s before and after prostate surgery. The scans measure the activity of microglia. Three months after the surgery, the cells’ activity had increased in four of the patients. The higher their activity, the worse patients performed on a mental test. “We can demonstrate that there is a profound change in the immune activity in the brain” after surgery, Eriksson says.

Inflammation may also spur postoperative delirium, says gerontologist Sharon Inouye of Harvard Medical School. The conditions may have something else in common. Delirium may set up the brain for POCD. Last year, anesthesiologist Finn Radtke of Charité Medical University of Berlin and colleagues found that patients who escaped delirium in the recovery room but then developed it within the next week were twice as likely to show POCD.

If surgery sets the brain afire, leading to POCD or delirium, can we douse it by giving patients anti-inflammatories during or after an operation? Although some human trials have reported that cyclooxygenase inhibitors similar to viox decrease the frequency of postoperative cognitive problems, many researchers shy away from those and other current inflammation-squelching drugs because of the risk of side effects.

“Anti-inflammatory approaches are very attractive, but they have significant limitations,” says neuroimmunologist Niccolò Terrando of Duke University Medical Center. Instead, he has tried activating the body’s natural mechanisms for shutting down inflammation, such as the vagus nerve, which serves as a brake on the immune system. He, Maze, and colleagues have shown that using a chemical to trigger the same immune effects as the nerve could prevent postoperative cognitive declines in mice.

Because people who are cognitively better off before surgery tend to stay that way afterward, other researchers are trying to determine whether boosting patients’ mental fitness through games or other brain workouts can forestall POCD. Such brain-training interventions might have helped Wahl, whose memory remains subpar more than a year after his last operation.

He continues to work part time and feels that his job performance hasn’t suffered. But to compensate, he had to make changes in his daily life. If he needs to remember something, he writes it down. And he always keeps his hockey sticks in the car so he won’t forget them. “I know I can’t trust my memory.” ■

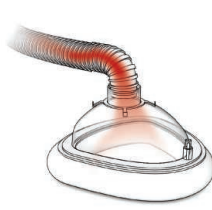
Why might surgery sap our brainpower?

How many surgical patients experience a cognitive decline after an operation remains uncertain, but here are some possible explanations.



Poor blood flow

Surgeries may curtail blood flow to the brain, triggering subsequent cognitive effects.



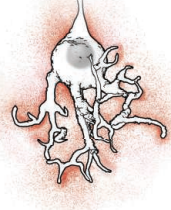
Anesthesia

Some data indicate that anesthetics can kill or harm brain cells, so they were an early suspect.



Preexisting conditions

Illnesses that lead to surgery may already be damaging a person’s brain before any operation.



Brain inflammation

Surgery sparks inflammation that may send harmful chemicals and cells into the brain.

recalls. “What was happening was that anesthetic was screwing up the brain in some way.” Many other researchers agreed. After all, in the culture dish, general anesthetics can kill neurons. Those drugs cause young animals’ brains to develop abnormally, and a growing body of evidence suggests that they stunt children’s brains. “If you see how [anesthetized] people awaken, it’s absolutely not normal,” says anesthesiologist Gregory Crosby of Harvard Medical School in Boston. They have a “disordered central nervous system,” he says.

Yet the data so far suggest that general anesthetic alone isn’t responsible for POCD. Surgical patients who receive local or spinal anesthesia also suffer cognitive problems, several studies have found. One 2013 paper found that, more than 7 years after the procedures, open-heart surgery patients scored slightly higher on cognitive tests than did people who underwent less invasive angioplasty, which requires only a local anesthetic.

Such studies don’t absolve general anesthetics, and researchers are investigating other potential POCD culprits, such as re-

Support for the hypothesis has come from animal studies—and some human results—suggesting that brain inflammation undermines memory and other important functions. Earlier this year, for instance, Maze and colleagues fingered microglia, brain immune cells that stoke inflammation, as possible players in POCD. Using a memory test they developed, they showed that eliminating those cells improves rodents’ recall ability. The test measures how long mice stay put after they are placed in a chamber where they previously received small electric shocks. Animals normally freeze for long periods, showing that they remember the environment and expect a jolt. Mice that have undergone leg surgery, however, remain immobile for less time, suggesting that their memories aren’t as strong. In the new study, published in *JCI Insight* in April, the researchers gave some of the operated-on mice a drug that kills microglia. Their memory remained intact: They froze for as long as control mice did.

One of the few brain imaging studies of people with POCD, reported this year in the

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