

First, do no harm

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Abstract:

Neurosurgeons began performing an operation designed to save lives in the 1970s, but the procedure actually put patients at risk and no one bothered to determine that for 20 years. The real problem was how fast the medical community embraced the extracranial-intracranial bypass without rigorous testing.

Full Text:

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FORSAKING THE HOT WAIKIKI BEACHES outside, several hundred neurosurgeons jammed the dark Honolulu lecture hall to await their featured speaker, Dr. Sydney Peerless. Just before noon he arrived, and as he strode onstage and switched on his slide projectors, the attendees of the thirty-fifth annual meeting of the Congress of Neurological Surgeons quickly fell silent.

I had interrupted my morning swim to squeeze into the back of the packed hall, my swimsuit still dripping-like many of my colleagues at the meeting, I spent more time bodysurfing than attending lectures. But this talk would be different; it would be surgical history in the making. The year was 1985, and Professor Peerless was about to pass public judgment on a popular brain operation known as the extracranial-intracranial (EC-IC) bypass. For eight years Peerless, a neurosurgeon then working in London, Ontario, had helped coordinate the giant clinical trial that was intended to prove once and for all that the operation worked as promised.

First performed on humans in 1967 by Dr. Gazi Yasargil and his colleagues in Switzerland, the EC-IC bypass was designed to take blood from the scalp and detour it into the brain. Yasargil believed this procedure would prevent strokes by beefing up the brain's blood supply. Because scalp and facial arteries rarely develop the hard fatty deposits (atherosclerosis) that normally clog aging blood vessels, elderly patients will often have excellent blood flow to every part of their heads except their brains. To redistribute the wealth more evenly, Yasargil devised a microscopic procedure for detaching scalp arteries and threading them through the skull, then suturing them to arteries on the brain's surface. These surgically created conduits would, he theorized, play Robin Hood, stealing from the rich scalp to feed the starving brain.

Yasargil offered his new operation to patients at high risk for future strokes, including patients with a history of strokes and patients with recurring bouts of temporary blindness, numbness, or limb weakness bouts known as transient ischemic attacks, which at the time were believed to be ominous warnings of impending stroke. From 1967 to 1976, Yasargil created bypasses in 84 patients. To his delight, he found that during that time only three had further strokes. Citing older studies of similar

patients published by other authors, Yasargil guessed that without bypassing, well over half his patients would have gone on to have more strokes. He concluded that the apparent reduction in future strokes from more than 40 to a mere 3 supported a "prophylactic role," or preventive use, for bypass surgery.

Of course, neurosurgeons hadn't exactly been holding their breath waiting for such results. They'd embraced the attractive concept of brain bypassing almost immediately-it seemed like a sure winner-and began offering it to their own patients years before any long-term data became available. By the time Yasargil published his small seminal study, several thousand bypasses had already been done. His results boosted interest further, and the Ec-Ic bypass quickly became a standard weapon in the war on stroke.

Microsurgical laboratories sprang up overnight to teach the fine skills required for joining spaghetti-size arteries with sutures invisible to the naked eye. Large hospitals and universities aggressively recruited experienced bypass surgeons. Technically elegant and very lucrative, the operation became the darling of the neurosurgical community.

Yet despite the enthusiasm for EC-IC bypassing among surgeons, there was concern about its unchecked use. Tiny studies like Yasargil's merely suggested that the operation prevented strokes. Where was the proof? Bypass opponents noted that surgically treated patients were being compared with untreated patients from earlier studies, a potential source of bias. They argued that only a head-to-head comparison of surgical and nonsurgical therapies would validate brain bypassing. To investigate the issue, the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) funded a grant proposal to measure both treated and untreated stroke rates simultaneously in the same patient population.

Beginning in 1977, the NINCDS persuaded 71 neurosurgical centers to assign high-risk patients randomly to two groups: one group to undergo EC-IC bypassing followed by daily aspirin therapy, the other group to receive daily aspirin therapy alone. (The power of aspirin to prevent stroke by reducing the risk of blood clots had already been demonstrated.) By the time it ended in 1985, almost 1,400 patients had been enrolled in the trial, which cost more than \$9 million. And now we sat, my colleagues and I, awaiting news of the trial's outcome. Unfortunately, rather than vindicate our operation, the study roundly condemned it.

Dr. Peerless told his stunned audience that the EC-IC bypass was, in a word, useless-in fact, a little less than useless. No matter how the investigators looked at the data, the stark conclusion remained: brain bypassing did not lower the risk of stroke. When investigators factored in deaths and strokes caused by the surgery itself, patients randomly assigned to the bypass group ended up with more strokes and a higher mortality-averaging an overall increase of 14 percent in nonfatal and fatal stroke-than those assigned to aspirin therapy alone. The operation didn't just fail-it made people worse.

Yasargil's beautiful theory died that day, slain by ugly facts. The now-wasted hours I had spent bypassing rat arteries flashed before my eyes. At the conclusion of the Honolulu talk, one of my colleagues approached me, cupped a hand to his ear, and lamented, "Did you hear that noise? The doors to a hundred microsurgical laboratories just slammed shut. For good." Bypass mavens fought hard to save their operation, but to no avail. After a brief and acrimonious debate over the validity of the NINCDS study, the bypass era finally ended. Insurance companies stopped paying for the operation, halting its use; many surgeons still believed in it, but not enough to do it for free.

Although a minuscule number of bypasses are still performed for two rare, life-threatening brain

diseases, the operation no longer has any role in the wholesale prevention of stroke. It now lies buried in the cemetery of dead therapies alongside bloodletting, head irradiation for ringworm, and a host of other harmful "cures." Yet for nearly two decades, the best brain surgeons on earth inflicted thousands of operations on unsuspecting patients in the mistaken belief that the procedure was helping them. In doing so, they caused more death and destruction than the disease itself.

How could they have been so wrong?

AS THE EC-IC BYPASS AFFAIR illustrates, experimental operations can jump into the medical mainstream long before anyone establishes their efficacy-or even their safety. Although ego and greed help keep unproved procedures in the operating room, it's bad scientific judgment that puts them there in the first place.

Admittedly, proving the worth of any experimental medical therapy can be an arduous task-and all the more so for surgical therapies. The most difficult operations to evaluate are those designed solely to reduce future risk. While the outcomes of most surgeries-like replacing a hip joint or closing a bullet holespeak for themselves, risk-reduction operations like the EC-IC bypass change the future likelihood of an undesirable event such as stroke, heart attack, or cancer metastasis. They often do little or nothing to make patients feel better right away, so neither the patient nor the surgeon has any immediate sense of whether the operation works. Since most diseases, including many cancers, progress slowly, it can take years before the impact of surgery on a disease process becomes apparent. Advocates of new risk-reduction surgeries must therefore test their procedures in large numbers of patients and follow them carefully for many years, a costly and timeconsuming job.

The risk of surgical complications makes the job even harder. Many brain bypass candidates were elderly hypertensive men with coronary artery disease in addition to their severe cerebrovascular disease-no healthy marathoners in this group. Repairing their hernias would be risky, let alone subjecting them to cranial microsurgery lasting many hours. Not surprisingly, Yasargil's surgery caused the death of 3 of his first 84 patients and maimed another 2.

Because of the dangers, risk-reduction operations present patients with a quid pro quo: take a chance of disaster today in exchange for a reduced chance of disaster tomorrow. But how can the surgical reduction of future risk be measured, given that the future hasn't happened yet? This requires a comparison of longterm outcomes in surgical patients with outcomes in untreated patients.

The untreated (control) patients can be obtained retrospectively, as Yasargil had done, by looking up earlier studies of patients with untreated cerebrovascular disease. Since these patients exist only on paper, it costs nothing to evaluate and treat them. Unfortunately, no past ensemble of patients can be configured to look precisely like the surgically treated group. Not only do they belong to a different era, but they may also come from different cities, even different countries, and often have different lifestyles.

The NINCDS study, on the other hand, accumulated its own controls as it went along. Using sophisticated computer randomization, control groups can be crafted to resemble the surgically treated group down to the tiniest detail. Even better, these controls will be evaluated at the same time and by the same doctors as the operative patients.

As in any scientific experiment, poor controls lead to wrong conclusions. Consider a hypothetical example from the business world. A security company plans to market a new home alarm system. First it installs the system in 1,000 homes, and during the ensuing year it finds that 5 of the homes have been

burglarized. Then the company researches the burglary rate in "comparable" homes without security systems and calculates that its 1,000 homes should have had 20 robberies in one year rather than 5. Conclusion: The system reduced the burglary rate by 75 percent.

But a competitor contends that the study is flawed because it used outdated home burglary rates for comparison. The competitor repeats the study by choosing 2,000 homes, installing working alarm systems in 1,000 chosen at random. In the other 1,000 homes, the company installs sham systems. The new study confirms that 5 of the homes equipped with the real system will be ransacked in one year—the first study got that much right. However, only 5 homes with sham security systems are robbed as well, not the 20 predicted by the first study. The presence of an alarm system didn't alter the burglary rate.

The first study's mistake lay in comparing the current annual home burglary rate with a statistic from five years earlier, when the overall crime rate was higher. Advocates of the EC-IC brain bypass made a similar mistake by attributing their low postoperative stroke rates to the EC-IC bypass rather than considering the possibility that they didn't fully understand the disease they were treating. The low postoperative stroke rate observed by Yasargil and others merely reflected the natural stroke rate of that era and had nothing to do with the surgery. The operation only appeared to work because surgeons initially compared their operative patients with patients from small retrospective control groups who happened to manifest a higher natural incidence of stroke.

YET THE BLAME CANNOT BE laid on Yasargil. He had invented an elegant operation that appeared to offer a safe strategy for avoiding stroke. His retrospective study was, in fact, no more flawed than any other. The real problem was how quickly the medical community embraced the brain bypass without subjecting it to the kinds of rigorous testing required for drugs or surgical devices.

Before any new drug can be marketed in the United States, the Food and Drug Administration mandates that it pass three levels, or "phases," of human clinical testing. In Phase I the drug is given in escalating doses to brave volunteers just to see how well the drug is absorbed and how toxic it might be. Once a safe dosage has been established, the investigators try it on a group of diseased patients to see if they'll fare better than retrospective controls (Phase II). The early trials of brain bypassing were analogous to Phase II trials. If a drug looks promising in Phase II studies, it moves on to large-scale randomized trials (Phase III). Drugs succeeding in Phase III trials are candidates for FDA approval.

Although the FDA also regulates surgical devices like heart valves and pacemakers, it has no jurisdiction over surgical procedures. Unlike pharmaceutical companies, surgeons have no legal obligation to prove operations at the Phase III level before marketing them. Moreover, since they can bill for any surgery, proven or unproven, surgeons have scant incentive to subject one of their "cash cow" operations to randomized testing. The motivation for further testing usually comes not from those doing the surgery but from those paying for it: the federal government (via Medicare) and private health insurance companies.

There are, of course, natural brakes on the imprudent use of surgical procedures. A surgeon's concern about malpractice is one; worries about spiraling health care costs are another. Still, surgical procedures are routinely performed today without rigorous testing. One example is spinal fusion of degenerating disks to prevent back pain. Surgeons can remove a disk in a simple two-hour operation. Or they can remove the disk and, while they're at it, implant a steel plate—the theory being that it will help stabilize the spine. This procedure is more involved and costs two to three times as much as the simple disk removal. The problem is that while the plate may not harm the patient in the long term, there's no evidence that it's

any more effective than the simpler procedure.

Surgeons make money, surgical supply companies make money, and patients are happy. There is little incentive to test a procedure further. After all, patients don't like randomized trials any more than their surgeons do. They go to surgeons to be treated, not to be assigned to "nonsurgical" groups by computerized coin tosses. If denied surgical therapy through randomization, patients may feel cheated and seek surgery outside the study. Critics of the EC-IC bypass trial pointed out that many of the best bypass candidates jumped ship and had their bypasses elsewhere. In pharmaceutical studies, patients who don't agree to randomization have no chance of getting the experimental drug.

Randomized trials have their downside. They cost tons of money, take forever, and crank out a bunch of statistical jargon hardly anyone understands. Doctors treat patients, not probability distributions, and they may not believe the results of the trials anyway. Ethicists moan that control groups, by being denied a promising therapy, may not be getting "state of the art" care. Patients have trouble understanding why their medical therapy falls to chance.

But without randomized trials I would still be harming people with brain bypasses. General surgeons would still be mutilating women with radical mastectomies instead of removing only the cancerous lesion. And thoracic surgeons would still be ligating mammary arteries-a procedure once thought to relieve angina by increasing blood flow into the heart-instead of doing things that really work. How many popular operations of today will wither in the glare of randomized testing tomorrow?

Some activists complain that randomized evaluation of medical therapies takes too long and should be abandoned in favor of "fast track" testing. Unfortunately, randomized testing represents the best science we have.

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