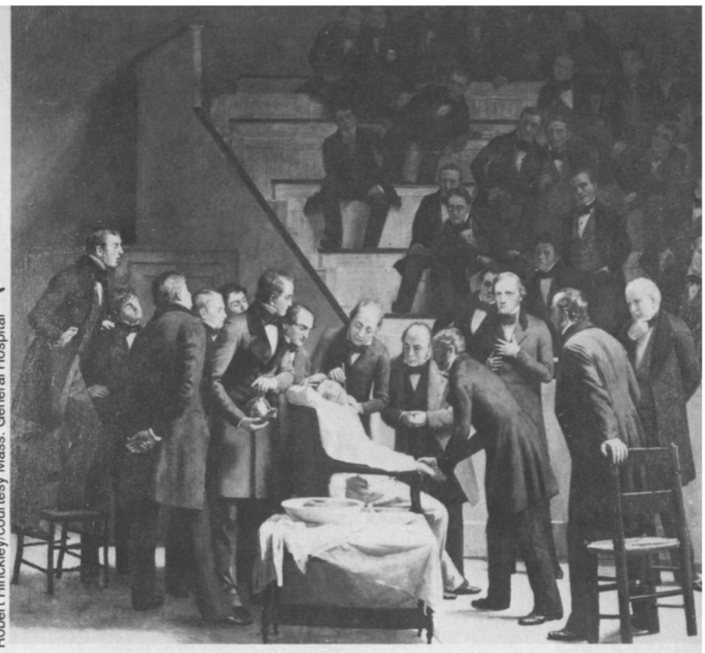
Awakenings in Anesthesia

Amid controversy, scientists move closer to understanding surgery's mysterious partner



Robert Hinckley/courtesy Mass. General Hospital

Formerly requiring strength and speed, surgery under anesthesia became a careful process for exploration and repair. Here, in 1846, William Morton performs the first public operation using a general anesthetic.

By LAURA BEIL

The anesthesiologist inspects a syringe against the light, and tells the patient strapped to the operating table she will soon be drowsy.

"Just try to relax," he whispers, partly to reassure her that she will not be alone while under the most dangerous drugs in modern clinical use. His eyes will watch the rhythmic streaks of her heartbeat on a monitor overhead, and when the gas has made her lungs forget to breathe, he will remind them of their job.

The administration of anesthesia, refined by decades of trial and error, is undertaken in the United States 25 million times each year. First, a sodium thiopental injection knocks out the patient so fast that, should she try to count backward from 100, she will not reach 97. The drug is rapid but short-lived. The two-hosed mask covering her nose and mouth delivers the right concoction of oxygen and two other anesthetics that will keep her free from pain, consciousness and memory for the next few hours. Meanwhile, the anesthesiologist will be the surgical equivalent of an airline pilot, enabling the passenger to hover safely between sleep and coma.

It has been more than 140 years since general anesthetics made their debut in traveling ether shows and the parlors of wealthy folk who took long drags of laughing gas (nitrous oxide) for recreation. In 1842, Georgia physician Crawford Long performed probably the first painless surgery on an etherized patient, and four years later, dentist William Morton demonstrated the procedure for astounded onlookers at Massachusetts General Hospital.

But as the surgical technique of anesthesia has crystallized, our understanding of it has remained clouded. A few injectable narcotics that can act as anesthetics — namely opiates such as morphine and codeine — have known, lock-and-key receptor sites. The mechanism behind inhalation anesthetics, however, is not as easily explained. Compounds of various sizes and shapes induce unconsciousness, with their ability to dissolve in lipids (as opposed to dissolving in water) being the main thing they have in common. Most are gases or volatile liquids of small molecules, like the three commonly used in hospitals: halothane, isoflurane and enflurane.

No theory of anesthetic action has been universally accepted. As Leonard Firestone of the University of Pittsburgh puts it, "We know how to exploit anesthetics. We know that they work. We're just not sure how."

Research is gradually closing in on the answer, however. Scientists now group themselves into those who believe anesthesia molecules have a specific, as-yet-unidentified target site on the surface of cell membranes, and those who believe they act more generally within the membrane.

Throughout the double film of the lipid molecules that form cell membranes, proteins protrude like icebergs from a sea. These proteins give membranes their character, and help nerve impulses leap from cell to cell by channeling ions through the membranes. Since anesthetics disrupt the transmission of nerve impulses, they must ultimately obstruct the membrane proteins. That much is agreed on.

Scientists in the specific-action school of anesthetic research — also known as protein theorists — believe a binding site for anesthetics probably lies somewhere directly on the proteins themselves. General-action, or lipid, theorists insist the anesthetic, by dissolving in the membrane lipids, affects proteins secondarily as they float in this lipid-anesthetic sea.

The first evidence for the lipid theory, says Harvard Medical School's Keith Miller, emerged at the turn of the century with the discovery that all inhalation anesthetics are lipid-soluble. "The solubility enables you to predict their potency," he explains. Indeed, the relationship is almost exactly linear: The more easily an anesthetic dissolves in a lipid solvent, the less it takes to induce an anesthetic state. Chloroform and halothane, two of the most powerful inhalants, dissolve very readily in a lipid such as olive oil.

But that relationship "is totally coincidental," contends Nick Franks, of the Imperial College of Science and Technology in London, England. Along with colleague Bill Lieb, Franks has published paper after paper pointing to membrane proteins as the direct target site for anesthetic molecules. Most recently, the two reported in the June 16 NATURE that some pond-snail nerve cells were more sensitive to anesthesia than others, and that this sensitivity reached a saturation point at a low level. Selectivity of action and easy saturation are two characteristics of a cell with a limited number of receptor sites.

"It's consistent with the [protein] theory, but it's not conclusive," Franks says of the snail-neuron research.

Protein theorist Alex Evers of Washing-

ton University in St. Louis has used nuclear magnetic resonance (NMR) to trace the path of anesthetic molecules as they seep into the brains of rats. He reported in the July 9, 1987 NATURE that halothane quickly reaches a saturation point among cells in the brain. If the molecules were merely dissolving in the membranes, the amount of anesthetic exposed to the cell should correlate almost exactly with its solubility in lipids, he says. For this experiment, it didn't.

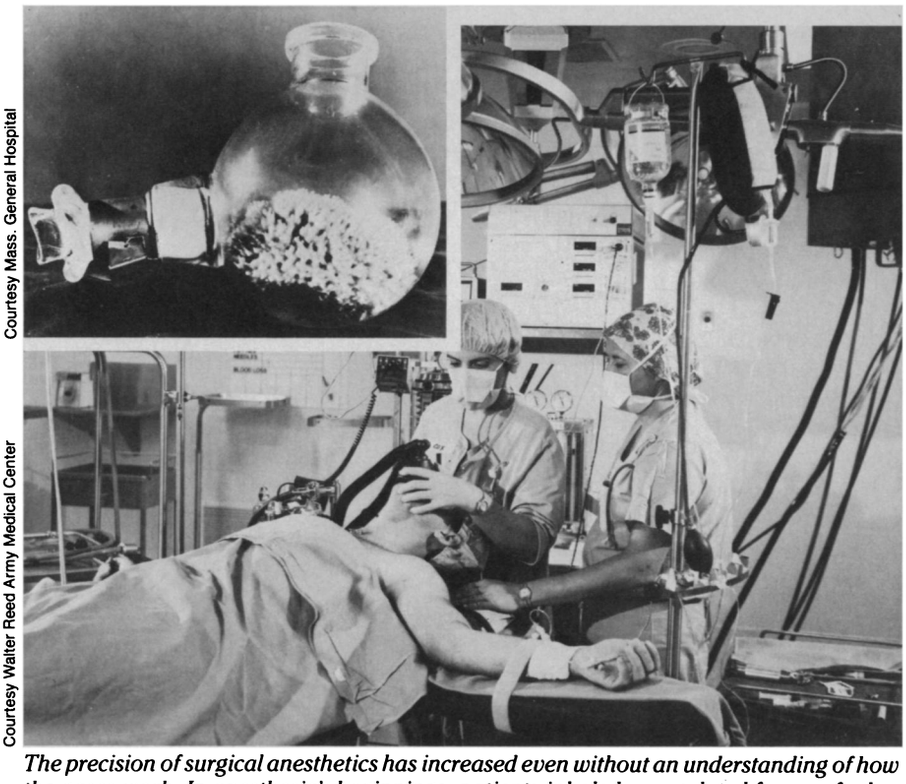
Moreover, Evers' NMR spectroscopy showed that anesthetic molecules behaved in two different ways after they reached the cell. Some molecules were stationary, while others moved around. "The more mobile molecules correlated with lipid interaction," Evers says, meaning the halothane molecules pooled in the lipid membrane could tumble freely. But other molecules remained glued to what Evers believes is a binding site. Supporting that hypothesis are data showing those immobile sites were filled first and could produce unconsciousness regardless of the amount of anesthetic dissolved in the lipid portion of the membrane.

The lipid theory is buttressed by a number of phenomena that have remained unexplained for decades. One of them is, as mentioned earlier, that anesthetics work despite their small molecular size and variety, decreasing the likelihood of a uniform receptor. Another is a peculiarity discovered 40 years ago called "pressure antagonism," which is another way of saying extremely high pressure reverses anesthesia.

Simplistically speaking, a person must have normal-sized membranes for consciousness. When an anesthetic dissolves in the cell membrane, it increases the membrane's volume and expands it slightly. Some lipid theorists say high pressure pushes the membrane back to its original dimensions, counteracting the anesthetic's effects. Others suggest pressure squeezes the anesthetic out of the membrane like water out of a sponge (SN: 2/20/88, p.126) or slows its movement through the lipid layer, preventing it from ever reaching the proteins controlling ion transport.

In the spirit of compromise, a third and growing group of anesthesiologists has suggested general anesthetics have a protein-lipid dual action. "The combination of the two is my favorite," says Firestone of the University of Pittsburgh, who began preliminary spectroscopic work as a postdoctoral researcher in Miller's laboratory at Harvard. "Anesthetics may have their most important action in between the protein and the lipid. I'm not copping out; this really seems to be the most sensitive area."

And even Miller, well known as a lipid theorist, has softened his stance. "The two theories may end up converging in the end," he says.



Courtesy Mass. General Hospital

Courtesy Walter Reed Army Medical Center

The precision of surgical anesthetics has increased even without an understanding of how the gases work. In anesthesia's beginnings, patients inhaled unregulated fumes of ether from a saturated sponge (inset).

Whatever their specificity at the molecular level, anesthetics intoxicate every excitable cell in the body. Most pronounced is their relationship with the central nervous system. Protein theorists explain this by saying the brain and spinal cord must then contain more target sites for the drug. Lipid theorists say the brain is the area most affected when anesthetics block transmission of nerve impulses throughout the body, because it relies more on nervous transmission than do other tissues.

Studying either possibility is not an easy job. Spectroscopy can provide a window into the behavior of anesthetics in the nervous system, as it does with cell membranes. Lawrence Litt of the University of California, San Francisco, himself a general-action theorist, reported in the August 1987 ANESTHESIOLOGY on the uptake and elimination of halothane and isoflurane from the brain. After breathing halothane for an hour, rats eliminated it relatively quickly (in about 90 minutes) from their brains. Rabbits that breathed isoflurane for an hour and a half also eliminated the anesthetic quickly, with about half of it disappearing in the first 30 minutes after the gas was shut off. Although Litt's study provides some of the latest information on how anesthetics affect the brain, more neurological research could streamline dosage decisions.

Litt says there are problems detecting anesthetic in more detail in whole, living brains because anesthetic molecules, as a consequence of their affinity for lipids, tend to migrate toward the fatty tissue, muscle and bone marrow near the scalp. Spectroscopic measurements are then overwhelmed by the anesthetic on the outside of the brain, not the inside.

One other curiosity of anesthesia's effect on the nervous system: It wears off in a person's spine while the brain is still asleep. This was demonstrated last February by a team led by Daniel Sessler, also of the University of California, San Francisco (SN: 3/12/88, p.168). He says the result is a period of time when the spine becomes chemically isolated from the dozing brain, resulting in the uncontrollable shaking experienced by about half of all patients as they wake from surgical anesthesia.

"The clinical process right now is more of an art than a science," says Stanford anesthesiologist Donald Stanski. Anesthesia's dosage and timing, he observes, are in the hands of doctors and nurses using drugs that no one completely understands. Adds Litt: "The problem clinically is that they don't send us the same patient every time."

When pressed, most researchers in the field will say that as a group they are only about 10 years away from understanding anesthetics. As Firestone notes, regardless of how many researchers support one particular theory of action, science is not decided by majority vote. "It's like convicting someone of murder: You want to be sure beyond a shadow of a doubt," he says. And when researchers finally are sure, medicine's most mysterious drugs will become much more science than art. □