ANESTHESIA

Chemistry in the Operating Room

By Claudia M. Caruana

Throughout history, people have sought ways to relieve suffering. Many substances that control pain were found serendipitously, sometimes by trial and error. As early as 4200 B.C., people discovered natural substances—often plants and plant roots—that could cause unconsciousness in animals and people, so they used them to relieve pain.

But it is only during the first half of the 19th century that people started testing chemical substances on patients for their use in medical surgery. Over the years, various substances were identified, and their effectiveness was compared. This work has led to an array of medicines that can numb pain locally or cause unconsciousness and decrease pain over the entire body.

Scientists and health professionals now have a good understanding of which anesthetics work best on patients, but they are still trying to uncover how these drugs operate at the cellular and molecular level.

Until the mid-1800s, undergoing surgery was excruciatingly painful because people would be awake during the operation. Thanks to drugs called anesthetics, all this pain and suffering is gone. How were these "miracle" drugs discovered and how do they work?

Local and general anesthetics

Anesthetics can be applied either to one area of the body—such as the skin, teeth and gums, or the spinal cord—or to the entire body. These two types of anesthetics, called local and general anesthetics, work by preventing nerves from carrying pain signals to the brain. This way, the brain does not perceive pain.

Local anesthetics can be given by injection to numb parts of the body during surgery and dental procedures. They can also be used to numb the eye before certain eye examinations—typically, when eye doctors measure eye pressure or remove stitches or foreign objects from the eye.

Other local anesthetics are available as ointments, sprays, or lotions to relieve itching, sunburn, insect bites, and minor cuts. They can even be taken orally to relieve throat pain or canker sores.

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General anesthetics are used during medical and surgical procedures that would be too painful to endure while awake. In addition to suppressing pain, as local anesthetics do, general anesthetics also induce a loss of consciousness that may feel like deep sleep. But unlike sleep, in which parts of the brain work by forming dreams and processing information, this loss of consciousness does not form dreams nor does it store memories.

Over the past centuries, people searched far and wide for substances with anesthetic properties. A substance that would shut down the entire body was the most sought-after type of anesthetic. The pain from surgery and other medical procedures was often more excruciating than that from the local treatment of a wound or a dental procedure. So, medical personnel tested many different substances on patients, sometimes with unexpected side effects.

Nitrous oxide

One of the most well-known and most successful general anesthetics is nitrous oxide (N_2O). It was discovered at the end of the 18th century and is still being used in surgical anesthesia.

Nitrous oxide is a colorless, almost odorless gas that was first discovered in 1793 by an English scientist and clergyman named Joseph Priestley. Following Priestley's discovery, British chemist Humphry Davy realized that nitrous oxide had physiological effects. He noticed that people who inhaled it started laughing for no reason, and he called it "laughing gas."

Davy realized the anesthetic effect of the gas, but for the next 40 years, the main use of nitrous oxide was in traveling medicine shows and carnivals. People would pay for inhaling small amounts of the gas and would laugh and act silly until the effect of the drug wore off. Nitrous oxide found a more scientific use as an anesthetic in dentistry and medicine in the early 1840s.

Other general anesthetics

Nitrous oxide is still used as a general anesthetic in combination with other chemicals. But its main use is as a mild sedative and a pain reliever, because nitrous oxide can cause the lungs to collapse and can lower the oxygen content of tissues.

Most of the other general anesthetics used today are administered through the lungs and thus are called inhalation anesthetics. The first widely used inhalation anesthetic was diethyl ether ($C_2H_5OC_2H_5$), a highly flammable liquid, especially in the presence of oxygen. Diethyl ether increases the risk of fires, or even explosions, in operating rooms during surgeries, so this compound has fallen out of favor.

Today, halogenated ethers have replaced most other compounds for use as inhalation anesthetic. An ether is an organic molecule that contains an oxygen atom connected to two organic groups. Its general formula is R-O-R', where R and R' are the organic groups. A halogenated ether is an ether in which one or more hydrogen atoms are replaced with halogen atoms (fluorine, chlorine, bromine, or iodine).

Examples of halogenated ethers include isoflurane ($CF_3CHClOCHF_2$), desflurane ($CF_3CHFOCHF_2$), and sevoflurane ($CF_3CHCF_3OCH_2F$). Halogenated ethers have the advantage of being nonflammable and less toxic than earlier general anesthetics.

But not all halogenated ethers have an anesthetic effect. For example, flurothyl ($CF_3CH_2OCH_2CF_3$) has the opposite effect, by inducing convulsions and epileptic seizures. Flurothyl was previously used in psychiatric medicine for shock therapy, but this practice has been discontinued.

It's all in the chemistry

So, how do anesthetics work? When a painful sensation occurs—due to, say, a wound or a teething pain—nerve cells send a message

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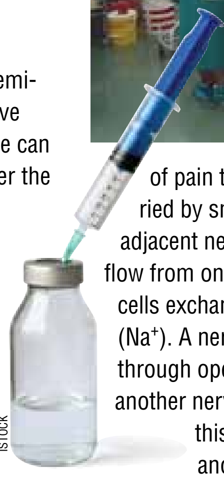

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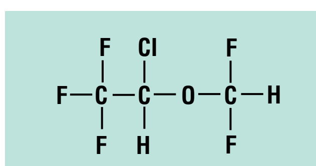
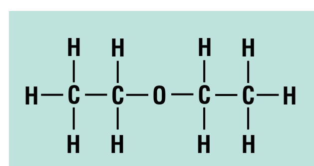
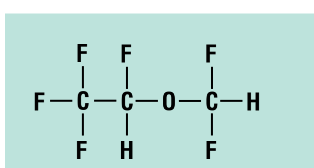
of pain to the brain. This message is carried by small electrical currents through adjacent nerve cells. For these currents to flow from one nerve cell to the next, the nerve cells exchange ions, such as sodium ions (Na^+). A nerve cell will release these ions—through openings on the cell surface—and another nerve cell will capture them. Then, this nerve cell will do the same with another nerve cell, and so on.



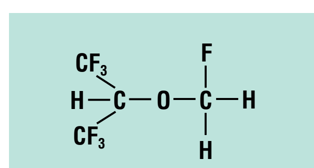
Isoflurane



Diethyl ether



Desflurane



Sevoflurane

Anesthetics work by preventing sodium ions from going from one nerve cell to the next. But the details of how this is done are not well known. An easy explanation would be that the anesthetic molecules bind to a nerve cell and block the openings through which the sodium ions are released. But this is not what happens.

Scientists have observed that the anesthetic molecules do not bind to nerve cells, so the sodium ions are released. But somehow, these ions are not captured by other nerve cells, preventing them from carrying the pain signal to the brain.

The way general anesthetics work is even more mysterious. Not only do these anesthetics prevent pain signals from reaching the brain, but they also cause unconsciousness and memory loss. Scientists hope to find answers by comparing what happens at the cellular level during general anesthesia, actual loss of consciousness (say, due to a stroke) and amnesia (a medical condition that causes memory loss).

"It's still a black box," says John Stork, a pediatric anesthesiologist at Babies and Children's Hospitals, Cleveland, Ohio, and a professor of anesthesiology at Case Western Reserve Medical College in Cleveland. "But there is considerable research going on to help anesthesiologists understand how anesthetics affect the body at the cellular level."

General anesthetics also cause side effects, such as nausea and pain, so doctors provide antinausea drugs and painkillers to patients. But how these side effects happen is not well understood. What physicians know is that during surgery, stomach acids build up because of the many drugs given. Physicians and scientists are investigating what this build-up of stomach acids does to the body; they are also looking at other changes in the body that could cause nausea and pain.

Anesthesia has relieved surgery patients from all the pain and suffering that they would feel otherwise during surgical procedures. The next step will be for scientists to unravel the details of how anesthetics work at the cellular level and to find ways to prevent their side effects from happening.

SELECTED REFERENCES

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