Editorial

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180th Anniversary of Ether Day

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Epitaph on the tomb of William Thomas Green Morton. *"Inventor and revealer of inhalation anesthesia: Before Whom, in all time, surgery was agony; By Whom pain in surgery was averted and annulled; Since Whom, Science has control of pain."*

In ancient times, pain during surgery was expected–a form of suffering patients had to endure despite the use of high doses of alcohol, opium, mandrake, and other failed attempts of anesthesia–analgesia. Pain–free surgery became a reality in 1846 with the introduction of ether by Thomas Morton, who demonstrated that it was possible to perform operations while the patient was in a deep, painless sleep. This milestone marked the birth of modern anesthesiology, transforming medicine forever. Since then, our specialty has advanced by leaps and bounds; ether has been replaced by safer gases and by rapid–acting intravenous anesthetic, as well as neuromuscular blocking agents. Cocaine paved the way for regional anesthesia, a field that–much like general anesthesia–evolved rapidly with the invention of innovative local anesthetics and adjuvant drugs. This history is rich in anecdotes and breakthroughs; in the modern era, these advancements have not only facilitated complex surgeries but also optimized patient safety, postoperative care, treatment in critical care units, emergency departments, pre–hospital settings, disaster zones, as well as the comprehensive management of acute and chronic pain, alongside research and teaching activities. Anesthesiology is currently transitioning from electronic monitoring of vital functions to the use of artificial intelligence as a valuable tool that extraordinarily enhances our professional capabilities.[1–5]

The evolution of anesthesiology features a definitive turning point that divides its history into two distinct eras: the period of pre–anesthetic surgery—characterized by severe pain, psychological trauma, and technical limitations that frequently resulted in serious complications or perioperative death—and the era of modern anesthesiology, defined by physiological control, the elimination of suffering, and the feasibility of highly complex surgical interventions. Before the mid–19th century, entering an operating room was a terrifying experience akin to torture. Surgeons were not valued for their meticulousness or detailed anatomical knowledge, but rather for their extreme speed; a patient's survival depended directly on how many minutes the operator took to amputate a limb or remove a tumor or gallstone. For millennia, pain was considered an intrinsic component of human experience and, specifically, an unavoidable price to pay for surgical healing. Medical literature from antiquity –ranging from Egyptian treatises to texts from Classical Greece and the Middle Ages – documents a desperate search for substances capable of alleviating suffering, albeit with markedly limited success. Several civilizations resorted to botanical extracts and alcoholic mixtures to mitigate the unbearable suffering of surgical interventions. In Greece, during the 5th century BC, the historian Herodotus described how the Scythians inhaled cannabis vapors to alter consciousness, while in 3rd–century AD in China, the famous surgeon Hua T'o combined this herb with wine to numb his patients. Likewise, in 1st–century AD the Greek physician Pedanius Dioscorides formally documented the analgesic properties of opium, henbane, and mandrake, coining the concept of insensibility prior to operative incision. Subsequently, in the 13th century, the Italian monk Theodoric of Cervia refined the famous soporific sponge at the ancient University of Bologna, infusing these same botanical substances dissolved in alcoholic solutions to dull pain during operations, marking a fundamental milestone in medieval pharmacological practice.[2–6]

Surgeons of antiquity relied on rudimentary and dangerous pharmacopeia. Among the most widely used agents were:

a) Opium (Papaver somniferum): Employed since antiquity in crude formulations, liquid extracts, or alcoholic preparations such as laudanum, it offered a degree of sedation and analgesia. However, prior to the chemical isolation of its active alkaloid, the potency of these botanical concoctions could neither be predicted nor standardized. Consequently, its narrow therapeutic index presented critical risks: subtherapeutic doses failed to prevent the severe pain and neurogenic shock induced by acute surgical procedures, whereas slightly higher quantities frequently triggered fatal respiratory depression and irreversible deep narcosis, ultimately failing as a reliable anesthetic agent.

b) Mandrake (Mandragora officinarum): Valued since antiquity and classical Greco–Roman medicine for its profound sedative properties, this solanaceous plant contains high concentrations of potent anticholinergic tropane alkaloids, primarily scopolamine, hyoscyamine, and atropine.[7] Administered in herbal infusions or wines to induce surgical stupor, its clinical utility was severely constrained by an unpredictable dose–response profile. The concentration needed to achieve adequate surgical analgesia competitively blocked central and peripheral muscarinic receptors. Consequently, patients frequently suffered from toxic anticholinergic syndrome –manifested by extreme tachycardia, hyperthermia, urinary retention, severe agitation, vivid hallucinations, and prolonged central nervous system delirium–rendering it a dangerous and unreliable anesthetic agent.[8]

c) Alcohol and mechanical trauma: Prior to the advent of predictable

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anesthetics, practitioners occasionally resorted to extreme physical interventions in desperate attempts to blunt surgical pain. Intoxicating quantities of ethanol were ingested to induce an alcoholic comatose state; however, the massive doses needed to eliminate nociception severely depressed vital autonomic centers, frequently causing lethal respiratory arrest or cardiovascular collapse. Similarly, in military or emergency settings, surgeons attempted to induce transient unconsciousness through partial asphyxiation via carotid artery compression or by inflicting blunt cerebral concussions. Ultimately, these crude modalities carried prohibitive risks of permanent neurological trauma, severe systemic morbidity, and fatal outcomes, failing as reproducible anesthetic techniques.[9]

d) Laudanum: Derived etymologically from the Latin verb *laudare* ('to praise'), laudanum originally constituted a hydroalcoholic solution containing roughly 10 percent crude opium, introduced during the European Renaissance by Paracelsus and later refined by Thomas Sydenham. Long before the discovery of modern inhalation anesthesia or synthetic opioids, historical physicians relied heavily upon this potent, versatile pharmaceutical formulation as humanity's principal sedative and analgesic to alleviate severe pain, insomnia, and acute gastrointestinal distress.

In addition to these rudimentary pharmacological approaches, patients were restrained by strong assistants responsible for "providing anesthesia"—often supplemented by applying intense cold to the surgical site—or simply by striking the patient on the head until they lost consciousness. Biting down hard on a piece of wood or leather was another method used to help these unfortunate patients endure the pain of surgery. Neurogenic shock, hemorrhage, sepsis, and death were common during the postoperative course in that archaic era. The lack of effective analgesic methods drastically limited the scope of surgery. Procedures were confined to superficial interventions, the drainage of abscesses, wound cauterization, and limb amputations. Internal cavities—abdominal, thoracic, and cranial—remained virtually unexplored, as opening the body of a conscious patient triggered a massive sympathetic response that was impossible to control. Those who survived the surgery were left with profound physical and psychological consequences, equivalent to modern post–traumatic stress disorder.

Paradoxically, the discovery of ether dates back to 1275 AD, when the Catalan philosopher and alchemist Ramon Llull (1232–1315) first described it. Later, in 1540, it was synthesized by the Prussian botanist Valerius Cordus (1514–1554), who distilled sulfuric acid with fortified wine to create *oleum vitrioli dulce* (sweet oil of vitriol). Around that same time, Paracelsus recognized the analgesic properties of ether. Nitrous oxide was synthesized in 1772 by the English chemist Joseph Priestley (1733–1803) – to whom the discovery of oxygen is also attributed. The modern era of anesthesia spans 180 years of an interesting and controversial history –filled with anecdotes, experiments, failures, and significant advances– that have shaped patient safety both inside and outside the operating room. At the dawn of the 19th century, the scientific community began experimenting with various gaseous substances in an effort to control surgical pain. As early as 1799, the British chemist Humphry Davy had identified the analgesic properties of nitrous oxide and even suggested its use in surgery; however, his observations were ignored by the medical community, and the gas ended up being relegated to public spectacles and traveling fairs as "laughing gas." Similarly, Crawford Williamson Long, a physician from Georgia, USA, used diethyl ether in 1842 to remove small tumors from patients but did not publish his findings immediately, thereby depriving his discovery of the necessary global impact.[1–6]

The definitive setting for the birth of modern anesthesiology was Boston, Massachusetts. Horace Wells, a dentist who had attempted to demonstrate the utility of nitrous oxide for tooth extraction at Massachusetts General Hospital in 1845, suffered a public failure when the patient screamed in pain during the procedure, drawing jeers from the students and physicians present. This failure, however, spurred on his former partner, William Thomas Green Morton. A year later, aware of the limitations of nitrous oxide and of his friend Well's failure, Morton sought the advice of chemist and physician Charles T. Jackson, who suggested using highly purified diethyl ether. After conducting successful experiments on animals and himself, Morton designed a glass inhaler that allowed for the regulation of ether vaporization. Finally, on October 16, 1846, Morton performed the demonstration that would change the course of human history. In the surgical amphitheater of Massachusetts General Hospital (known today as the Ether Dome), he administered vaporized ether to patient Gilbert Abbott, and surgeon John Collins Warren—the hospital's chief—removed a vascular tumor from Abbott's neck in a completely calm, painless procedure! At the conclusion of the surgery, a deeply moved Dr. Warren addressed the skeptical audience of physicians and students, pronouncing the famous words: "*Gentlemen, this is no humbug.*"[1–3]

Although the ether anesthesia demonstrated on that memorable day was irrefutable, there was a fourth patient –Betsey Magoun, also operated on at the same hospital– who suffered hypoxia and postoperative complications that endangered her life, generating uncertainty about the use of ether.[10] Nevertheless, the news of painless surgery had a global impact that spread with remarkable speed for that epoch. Within a few months, the use of ether was adopted in major hospitals across Europe and the Americas. Oliver Wendell Holmes Sr., a prominent physician and writer of the era, dean of the Harvard Medical School, coined the term "anesthesia" (from the Greek *an–*, meaning "without," and *aisthesis*, meaning "sensation") to describe this new state of induced insensibility.[11] This milestone not only alleviated human suffering but also transformed surgery from a harrowing, rudimentary practice demanding great speed and skill from surgeons into a precise medical science, allowing surgeons the time to thoroughly examine their patients and refine their surgical procedures.

Although the use of diethyl ether popularized painless surgery, it presented serious, critical drawbacks. It was a highly flammable and explosive substance, posing a constant danger in operating rooms lit by candles or gas lamps. Furthermore, it was associated with prolonged induction and recovery periods and caused severe adverse effects—such as intense postoperative nausea and vomiting—as well as respiratory tract irritation. Trichloromethane (Chloroform) was discovered independently in 1831 by the Frenchman Eugène Soubeiran, the German Justus von Liebig, and the American Samuel Guthrie, and was introduced into clinical practice by the Scottish obstetrician James Young Simpson in 1847; it rapidly gained popularity due to its superior potency and non–flammable nature. Its definitive acceptance was cemented when Dr. John Snow administered it to Queen Victoria of England during the birth of Prince Leopold in 1853.[12,13] However, chloroform soon revealed an alarming toxicity profile, characterized by a high incidence of fatal cardiac arrhythmias (a phenomenon known as "chloroform death") and fulminant hepatic necrosis.[14]

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In1868, surgeon Edmund Andrews improved nitrous oxide anesthesia by suggesting its combination with oxygen to prevent asphyxiation in patients. When administered in combination with oxygen, it demonstrated notably faster induction and emergence than ether, while simultaneously reducing the incidence of cardiopulmonary complications, and making it a safe and long–lasting anesthetic. However, its high risk of ignition and explosive nature led to its obsolescence.[15]

In the mid–20th century, the pharmaceutical industry revolutionized anesthesiology with the synthesis of fluorinated compounds; this drastically reduced flammability and improved the hemodynamic safety profile compared to the anesthetic gases known until then. The transition from the chemical instability of ether, chloroform, and ethylene to the development of safer, modern halogenated agents has been a vital step in the evolution of general anesthesia. This 20th–century pharmacological advancement can be divided into three major milestones based on safety profile, stability, and environmental impact. The development of halothane clearly marked a turning point in the history of general anesthesia. Synthesized by Charles Walter Suckling in 1951 and introduced into clinical practice in 1956 by M. Johnstone, R. Bryce–Smith, and H. D. O'Brien, it transformed the specialty by ushering in the era of non–flammable anesthetics. Unfortunately, its potential for hepatotoxicity limited its use and spurred the development of new fluorinated inhalational agents –such as methoxyflurane and enflurane– which were introduced in the 1960s. Subsequently, the development of isoflurane synthesized in 1965 and introduced in 1971, overcame many of these limitations, establishing itself for decades as the gold standard due to its outstanding cardiovascular stability profile.

The latest generation of anesthetic gases was synthesized in the 1970s; while this redefined the pharmacokinetics of these drugs, it also shifted the focus of medical attention toward their global ecological impact.

a) Sevoflurane (clinical use: 1990): Its low solubility allows for extremely rapid induction and recovery, positioning it as the agent of choice for mask induction in current pediatric practice.

b) Desflurane (clinical use: 1992): Despite its clinical properties, its use has seen a drastic decline in recent years. Under comparable Minimum Alveolar Concentration (MAC) conditions, desflurane has a global warming potential approximately 34 times higher per hour of anesthesia compared to sevoflurane, making anesthetic gases a critical source of greenhouse gas emissions.

The carbon footprint generated in operating rooms is a serious public health and global sustainability issue that has not received adequate attention. While the goal of hospitals is to heal patients, the healthcare sector is responsible for approximately 5.2% of global greenhouse gas (GHG) emissions, and the surgical department is by far the most resource–intensive area and the one with the greatest environmental impact. Volatile anesthetic gases are exhaled almost unchanged by the patient, pass through hospital scavenging systems, and are released directly into the atmosphere, where they act as potent greenhouse gases. In fact, medical gases account for up to 40% of an operating room's direct emissions.[16–18] This side effect of inhaled general anesthesia is, by far, the most harmful long–term drawback of William Thomas Green Morton's invention.

Alongside the pharmacological evolution of anesthetic gases, the introduction of curare, neuromuscular blocking agents, regional anesthesia, total intravenous anesthesia, and recently the use of Artificial Intelligence transformed anesthesia and surgical practice, making it safer. These advances shifted the specialty's conceptual paradigm, consolidating modern anesthesia. Consequently, the subsequent development of more selective agents helped minimize cardiovascular depression, facilitated increasingly complex surgical procedures, and established a robust physiological standard centered on hemodynamic stability and patient safety during the perioperative period.

Friday, October 16, 1846, at Massachusetts General Hospital in Boston, marked a watershed moment in the modern history of inhaled general anesthesia when William Thomas Green Morton successfully performed the first anesthesia using ether. Although Morton did not discover anesthesia –nor was he the first physician to attempt to alleviate surgical pain with ether or another inhaled drug– it was he who achieved this significant breakthrough before the right audience, with the correct patient, and in front of ideal spectators, thereby revolutionizing the evolution of medicine.

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