The history of therapeutic hypothermia and its use in neurosurgery

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Despite an overwhelming history demonstrating the potential of hypothermia to rescue and preserve the brain and spinal cord after injury or disease, clinical trials from the last 50 years have failed to show a convincing benefit. This comprehensive review provides the historical context needed to consider the current status of clinical hypothermia research and a view toward the future direction for this field. For millennia, accounts of hypothermic patients surviving typically fatal circumstances have piqued the interest of physicians and prompted many of the early investigations into hypothermic physiology. In 1650, for example, a 22-year-old woman in Oxford suffered a 30-minute execution by hanging on a notably cold and wet day but was found breathing hours later when her casket was opened in a medical school dissection laboratory. News of her complete recovery inspired pioneers such as John Hunter to perform the first complete and methodical experiments on life in a hypothermic state. Hunter's work helped spark a scientific revolution in Europe that saw the overthrow of the centuries-old dogma that volitional movement was created by hydraulic nerves filling muscle bladders with cerebrospinal fluid and replaced this theory with animal electricity. Central to this paradigm shift was Giovanni Aldini, whose public attempts to reanimate the hypothermic bodies of executed criminals not only inspired tremendous scientific debate but also inspired a young Mary Shelley to write her novel *Frankenstein*. Dr. Temple Fay introduced hypothermia to modern medicine with his human trials on systemic and focal cooling. His work was derailed after Nazi physicians in Dachau used his results to justify their infamous experiments on prisoners of war. The latter half of the 20th century saw the introduction of hypothermic cerebrovascular arrest in neurosurgical operating rooms. The ebb and flow of neurosurgical interest in hypothermia that has since persisted reflect our continuing struggle to achieve the neuroprotective benefits of cooling while minimizing the systemic side effects.

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FOR millennia, physicians have recognized the therapeutic effect of hypothermia on patients suffering neurological illness or trauma. Indeed, these attempts to preserve or rescue neural tissue are ultimately designed to preserve function. In more modern times, neurosurgeons have attempted to use surgery or specialized treatments to influence complex brain or spinal cord functions. History has shown this journey to be filled with tremendous promise and enormous pain.

Accounts of hypothermic patients seemingly miraculously recovering from typically fatal circumstances have piqued the interest of scientist-physicians for centuries, prompting many of them to carry out the early animal and human investigations that laid the foundation of our modern understanding of how cooling affects the central nervous system. As our understanding of the beneficial

and detrimental effects of hypothermia on human physiology and pathophysiology grew, so did our willingness to induce hypothermia in hopes of achieving better patient outcomes. Hypothermia was thus introduced into modern neurosurgery in the early 20th century, with promising early results. The Second World War posed a significant setback for hypothermia research, in large part due to negative associations with Nazi experiments. However, by the 1950s, cardiac surgeons and neurosurgeons had again begun experimenting with the effects of whole-body and local cooling. Recognition of the comorbidities conferred by moderate hypothermia led to a decline in interest through the 1970s, but interest re-emerged in the 1980s as a result of studies showing better risk-benefit profiles with mild rather than moderate hypothermia. The publication of clinical trials showing a benefit of induced hypothermia

ABBREVIATIONS BRL = Brain Research Laboratory; SCI = spinal cord injury; TBI = traumatic brain injury.

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following out-of-hospital cardiac arrest led to a permanent place for hypothermia in the resuscitation literature. In contrast, the neurosurgical literature has remained far more ambiguous regarding the utility of hypothermia as a neuroprotectant.

Pre-Modern History of Hypothermia in Neurosurgery

Antiquity

The Ancient Egyptians

Among the most legendary ancient Egyptian physicians was Imhotep (c. 2780 BCE), chief advisor to the pharaoh Zoser and regarded historically as an expert physician, surgeon, astrologer, architect, engineer, and priest. His accomplishments gained him the authority to design and oversee the building of the step pyramids at Saqqara, a position that many believe he used to systematically study the various injuries incurred by the slaves tasked with lifting the great stones used to construct the pyramids. Although Imhotep was never known to have recorded the results of his investigations, evidence exists to suggest that his medical teachings and wisdom were passed down for centuries and eventually recorded on the famous Edwin Smith papyrus.^{12,13,21,23,37,57,76,79}

The Edwin Smith papyrus is significant for many reasons. As the oldest medical text yet discovered, it details the origins not only of neurosurgical procedures, but also of plastic, orthopedic, and oral-maxillofacial procedures. More interesting, however, is how it was written as an objective, systematic guide to patient care with a focus almost entirely on physical treatments of disease rather than magical cures or protective prayers. The text reads as a 48-patient case series of injuries and other maladies commonly encountered at that time, organized from head to toe and from less to more severe. Each case begins with a title, and in each title is a hieroglyph meaning “knowledge gained from practical experience.” Each case is furthermore organized into history, physical, diagnosis, prognosis, and treatment—the earliest recorded evidence of our modern-day approach to patient care. At the end of each case comes 1 of 3 treatment suggestions based on prognosis: “an ailment I will handle,” “an ailment I will fight with,” or “an ailment for which nothing is done.” The papyrus is significant to the field of hypothermia as it contains the earliest historical evidence of our using the effects of cold to treat disease. Case 46, specifically, is a practical guide to the treatment of a noninfectious chest blister, “an ailment I will handle.” The recommended treatment is application of cool media. Considering the difficulty that ancient Egyptians likely had in discovering ways to keep things cool, the author included instructions on preparing this cool media: “Fruit, natron, and mineral, ground and bandaged on it; or calcite powder, mineral, builders mortar, and water, ground and bandaged on it.”¹³

Hippocrates

More than 1000 years later, the Hippocratic school of medicine was established in ancient Greece (Fig. 1). One of its particularly innovative diagnostic techniques was the covering of patients in wet mud and then watch-

FIG. 1. Engraving of Hippocrates (c. 460–c. 370 BCE) on the frontispiece of his famous work translated by Francis Clifton, “Upon Air, Water and Situation: Upon Epidemical Diseases: and upon Prognosticks, in Acute Cases Especially,” London, 1734. Image engraved by G. Van der Gucht from a drawing by Peter Paul Rubens of a bust of Hippocrates; the engraved image is a rendering of Hippocrates according to the artists’ imaginations. Figure is in the public domain.

ing to see which areas of the body dried first. The theory was that the mud would dry fastest in those areas with excess heat, and where there was excess heat, there was disease. In keeping with this theory, Hippocrates or associated philosopher-physicians became the first to induce hypothermia in patients as a form of treatment, specifically in patients suffering from tetanus, although these ideas changed over time. However, Hippocrates suggested that cold may have acute, regional effects as well: “cold should be applied in the following cases: when there is hemorrhage or the danger of one. In such cases apply the cold not to the actual spot from which the bleeding occurs or is expected, but round about.... Swelling and pain in the joints unassociated with ulceration, gout and spasms, are mostly relieved and reduced by cold douches and the pain thus dispelled. A moderate numbness relieves pain.”³⁴³

FIG. 2. Left: A woodcut from c. 1651 depicting the hanging of Anne Greene. A militiaman is depicted beating on her chest with the stock of his musket, and relatives pull on her feet in hopes of ending her misery more quickly. The upper left corner of the image depicts her resuscitation and rewarming. Right: William Petty (May 26, 1623–December 16, 1687) at the time of his election as professor of anatomy at Oxford. (Portrait by Isaac Fuller c. 1651.) Left panel: public domain. Right panel: © National Portrait Gallery, London. Used with permission.

Although theories at the time that cold and its effects on the human body were incomplete or unassociated observations of cause and effect, the Hippocratic school can be credited with affording us the first account of induced whole-body hypothermia as a treatment modality for systemic disease.^{1,36,42}

The Renaissance

Reports of hypothermia being implemented as a therapeutic agent are scarce throughout the Middle Ages and consist primarily of cold-water immersion as a treatment for various causes of fever.^{31,76,81} With the dawn of the European Renaissance came a marked increase in the number of accounts of positive outcomes following whole-body and local cooling (both accidental and intentional). For example, Girolamo Mercuriale was an Italian physician and politician who was infamously known for frequently interrupting the court of Emperor Maximilian II (to which he was invited as a court physician in 1573 and was named an imperial count palatine) to dash to the nearby River Arnus whenever he was overcome with a bout of renal colic. During these episodes, he could be found squatting in a particular spot in the river where a cold spring entered, allowing the chilled spring water to wash away his pain. He recommended the same treatment to many of his patients, who collectively became known as the “squatting figures of the River Arnus.”⁷⁶

A remarkable tale of survival after a hanging was reported in England in association with Thomas Willis. At the age of 22, Anne Greene of Steeple Barton, Oxfordshire, while working as a scullery maid for the household of Sir Thomas Reade, was impregnated by her master’s grandson. She kept the pregnancy a secret out of fear of

retribution and eventually gave birth to a premature still-born baby that she attempted to hide. The stillborn baby was discovered, however, and Anne Greene was convicted of murder. On December 14, 1650, she was hanged in the Oxford cattle yard before a large crowd. Just 15 years before her hanging, a law had been passed giving the body of any executed criminal within 21 miles of Oxford to the University of Oxford for the sake of medical education (medical students at that time were required to witness 2 human dissections and to perform 2 human dissections before graduating—and many were responsible for procuring their own cadavers). This law, known as the “reward of cruelty,” was intended not only to provide medical students with an anatomy education but also to slow down the grave robbers and resurrectionists who were running a burgeoning black market trade in human remains. Anne Greene’s remains were thus deemed to be the property of the University of Oxford, and she was scheduled to be dissected shortly after her hanging.

The day of her hanging was particularly cold for that time of year, with a temperature likely well below freezing. Anne Greene suffered a customary hanging for the period: with the noose tied around her neck, she was “then turned off a ladder” and allowed to hang for 30 minutes. Drawings show her beaten on the chest with a musket stock, while family and friends hung on her feet with their full weight, sometimes working together to lift her up and then drop her with a sudden jerk, hoping to end her misery quickly. The sheriff overseeing the event at one time ordered them to stop, fearing they would break the rope (Fig. 2 left). “After she had suffer’d the Law [passed the requisite 30 minutes on the rope], she was cut down and carried away in order to be anatomiz’d by some young

physicians.”⁷⁶ She was placed in a coffin, then taken immediately to the laboratory of William Petty (Fig. 2 right), who was head anatomy professor at the University of Oxford and working with Thomas Willis.

Several hours later, the coffin was opened, and to Petty’s and his assistants’ surprise, they saw Anne Greene breathing. Further inspection revealed a barely audible rattle in her throat and they dismissed plans for the dissection. Her breathing in the coffin was first perceived by a lusty fellow who “stamped on her breast and stomach several times with all the force he could,” and saw that she was “stretched out in a coffin in a cold room and Season of the year.”⁸⁰ The subsequent resuscitation actions, standard for the era, were to pour hot liquor down her throat, administer tobacco smoke enemas (a practice purportedly stemming from American Indian belief that tobacco smoke contains the spirits of life), drain approximately 5 ounces of blood, tickle her throat with a feather, rub her body vigorously, and place her “to bed to a warm woman.” After 12 hours she began speaking, after 24 hours she was answering questions freely, and after 48 hours her memory had returned except for the period of time surrounding the execution.

News of her recovery spread quickly. The courts decided to grant her a reprieve, reasoning that the hand of God had saved her and so they must cooperate. Oxford students took up a collection for her, and even composed humorous poetical accounts of her experience. Her father charged visitors admission to come and see her for themselves, which helped pay for her medical expenses and the legal fees for winning her reprieve. She later married, went on to have 3 healthy children, and lived 15 years after this lugubrious and shocking event.⁸⁰ Petty and Willis gained considerable fame for their success in resuscitating her.^{33,77}

Late 18th-Century Pioneers

During the latter years of the 18th century 2 pioneers in hypothermia research elevated the field from one of mere curiosity and case reports to a practice based on systematic observation and experimentation. John Hunter, appropriately known as the father of modern surgery, was regarded as an eccentric, enigmatic, and wildly controversial 18th-century physician (Fig. 3). As is the case with many unrecognized geniuses, Hunter was centuries before his time with regard to his scientific approach to inquiry; his conservative approach to surgery; and his revolutionary ideas on biology, evolution, and medicine. He spent much of his life on his farm outside London, where he housed the innumerable human and animal specimens he had gathered over a lifetime of study and where he also maintained a laboratory for testing the numerous theories and inquiries that kept him working throughout a standard 19-hour day. It has been plausibly suggested that Hunter provided the inspiration for the children’s book character Dr. Doolittle; both were eccentric country doctors whose fascination with natural history led them to study and treat all kinds of animals, both kept exotic animals in their homes, and both developed friendships with traveling circus owners to keep a steady source of new and rare animals to study. Hunter even went on to establish the Veterinary College of London in 1791.

FIG. 3. A portrait of John Hunter (February 13, 1728–October, 16 1793), who may be regarded as the father of modern scientific surgery. He carried out one of the first experiments to study the effects of hypothermia on live organisms and made many of the earliest discoveries in body temperature regulation and the physiological effects of hypothermia. Portrait by John Jackson, after Sir Joshua Reynolds, oil on canvas, 1813; copy of portrait by Sir Joshua Reynolds, made in 1786. © National Portrait Gallery, London. Used with permission.

Hunter had a lifelong interest in human resuscitation, reviving the dead, and searching for what he called the “living principle.” In his controversial but widely acclaimed “A Treatise on the Blood, Inflammation, and Gunshot Wounds,”³⁴ Hunter gave the following description of the living principle:

The principle upon which depends the power of sensation regulates all our external actions, as the principle of life does our internal, and the two act mutually on each other in consequence of changes produced in the brain. Something similar to the components of the brain may be supposed to be diffused through the body and even contained in the blood; between those a communication is kept up by the nerves.⁴⁶

In essence, Hunter believed that some substance produced by the brain and distributed throughout the body via blood vessels and nerves was responsible for life. Without that substance, living creatures are simply matter. Compiling the components of a being and arranging them in the appropriate fashion is not enough to produce life; the living principle is what was missing.

Hunter’s impetus for studying hypothermia arose from his deduction that only from life can we attempt to understand death, and so from death can we begin to understand life. His underlying goal was always to understand pre-

cisely what constituted life, where life emanated from, and what caused it to end. He, therefore, began studying life in suspended states of animation, the most common of which was hypothermia.

In 1766 Hunter began the most complete and methodical experiments on hypothermia yet performed. His experiments began with 2 carp he placed in a tub filled with snow and ice. To his and his assistants' consternation, they realized that the ice surrounding the fish kept melting. This led to his discovery that living beings generate heat, a realization that prompted further groundbreaking studies on the resting body temperature of various life forms. Eventually, he was able to freeze the carp to death, but upon rewarming, they remained lifeless. He froze many different types of animals using numerous methods, but he was always defeated in trying to resuscitate them. Eventually, he ceased attempting to revive frozen animals—a blow not only to the folklore that such reanimations were possible, but also to Hunter's naive ideas of making a fortune by offering his patients eternal life:

Till this time, I had imagined that it might be possible to prolong life to any period by freezing a person in the frigid zone, as I thought all action and waste would cease until the body was thawed. I thought that if a man would give up the last ten years of his life to this kind of alternative oblivion and action, it might be prolonged to 1000 years.... Like other schemers, I thought I should make my fortune by it; but this experiment undeceived me.⁴⁶

Hunter's experiments continued. Ten years later, he had successfully frozen rabbit ears and brought them back to full-blooded life. He tested the effects of cold on the hearts of animals, and he tested how long a heart could beat after it was removed from the animal (4 hours in frogs). His work eventually attracted the attention of William Hawes and Thomas Bogan, the founders of the Royal Humane Society (originally named the Institution for Affording Immediate Relief to Persons Apparently Dead from Drowning).^{14,59,60,68} They were interested in Hunter's theories on resuscitation, as they differed greatly from the standard bloodletting and tobacco smoke enemas.

In his typical manner, Hunter strongly opposed the accepted medical dogma and insisted that anyone (especially those found to be hypothermic) who suffered an untimely death without irreparable harm to vital organs could be brought back to life if rescuers acted quickly and appropriately. His recommended guidelines included first ventilating the lungs with a dual chamber bellows (which he invented) that allowed new air to be pumped into the lungs and old air let out. Furthermore, he recommended the use of the newly discovered dephlogisticated air (oxygen), if available, as this would likely be superior to room air or air expired from the mouth. Second, the patient should be slowly rewarmed, preferably in a bed. Finally, if no success was had with the first 2 steps, electric shocks could be administered in an attempt to restart the heart. Bloodletting and liquid or smoke enemas were recommended against, as Hunter believed that these methods were more likely to suppress rather than excite life. In describing his preferred method of resuscitation, Hunter essentially depicted the basics of modern cardiopulmonary resuscitation, 200 years ahead of his time. Furthermore, he not only recognized the importance of hypothermia in maintaining

the potential for life but also made many of the earliest discoveries in body temperature regulation and the physiological effects of hypothermia.^{14,46,59,60,68}

Around the same time that Hunter was performing animal experiments on hypothermia, resuscitations, and the living principle, Scottish physician James Currie began the first systematic human experiments of hypothermia.¹⁸ His professional interest in hypothermia began in medical school, but it was only after hearing news about a crew shipwrecked at sea that he committed wholeheartedly to this study. Following the shipwreck, 11 crew members were immersed in seawater for hours and survived, but the ship's captain and a passenger who were out of the water but exposed to wind and rain both died.

Currie's experiments eventually led him to the correct conclusion that heat loss from evaporation in the wind was responsible for the fate of the ship's captain and passenger. He conducted numerous experiments on volunteers and himself that involved monitoring body temperature, pulse rate, and respiratory rate during cold-water immersion; exposure to cold and wet wind; and the effects of rewarming. His work led to numerous discoveries, including the observation that, upon rewarming, the body temperature will often drop before rising, an effect we now know to be attributable to peripheral vasodilation. He furthermore borrowed thermometer technology from Hunter and made several important advances of his own in clinical thermometry that enabled the continuous monitoring of human body temperature in extreme conditions.²⁵

19th- and 20th-Century Pioneers and Theories

European society in the early 19th century had become fascinated with the topics of mortality, resuscitation, and the restoration of life to the dead. In the late 1700s, two Italian physicists and rivals, Luigi Galvani (Fig. 4A) and Alessandro Volta (Fig. 4B), captured the attention of many in Europe with their experiments on "animal electricity."^{26,29,74} Galvani hypothesized that the principle of animal electricity explained the effects of electricity on the legs of decapitated frogs when applied to the crural nerve. To Galvani and many of his students, he had seemingly developed a method for restoring life to dead frog legs, and he hypothesized that by applying electricity to certain areas of a dead body, one could produce circulation of a life-giving fluid (Hunter's living principle) throughout the nerves. He furthermore concluded that the brain housed this fluid and was responsible for circulating it throughout the body via peripheral nerves.

Volta was also an expert on electricity (he invented the voltaic pile and is the namesake for the unit of measure, the volt), but he disagreed with Galvani's theories and set about successfully discrediting him. Galvani's nephew and understudy, Giovanni Aldini, firmly believed in the ability of his uncle's work to restore life, and because of his exceptional communication ability in English, he spent much of his adult life attempting to restore his uncle's reputation by bringing galvanism to English society (Fig. 4C–E).^{2–4,24,45}

Aldini had developed a suave and showy method of demonstrating galvanism to an audience. He had performed numerous "resurrections" of cattle and even a

FIG. 4. **A:** Luigi Aloisio Galvani, Italian physician, physicist, and biologist, who studied bioelectricity (September 9, 1737–December 4, 1798). Anonymous painting, 18th century, University of Bologna. **B:** Galvani's rival, a famous Italian physicist and pioneer of electricity, Alessandro Giuseppe Antonio Anastasio Volta (February 18, 1745–March 5, 1827). **C:** Galvani's nephew, Giovanni Aldini (April 10, 1762–January 17, 1834). Aldini was a professor of physics who carried out animal and human experiments on galvanism, popularizing his uncle's invention for the English-speaking public. Portrait by William Brockedon, chalk and pencil, 1830. **D and E:** Illustrations from Giovanni Aldini's treatise on galvanism depicting his animal cadaver and human cadaver experiments with electricity (Aldini J: *Essai Theorique et Experimental sur Le Galvanisme, Avec une Serie D'Experiences*. Paris: De L'Imprimerie de Fournier Fils, 1804). Panels A and B: public domain. Panel C: © National Portrait Gallery, London. Used with permission. Panels D and E: Wellcome Library, London; copyrighted work available under Creative Commons Attribution only license CC BY 4.0 (<http://catalogue.wellcomelibrary.org/record=b1119983>).

small number of demonstrations on the limbs and heads of decapitated humans. Aldini realized in his early experience that people came to see his demonstrations as much for the show as for the science, and so he worked to give the audience what they wanted. Shortly after arriving in London, he contacted the Royal Humane Society, which was trying to convince physicians to support their mission statement of furthering the practice of resuscitation. Aldini figured that their support would help introduce him to members of London's more refined society, whom he had to convince of the legitimacy of his work. Although they were reportedly taken aback by his confidence, they agreed to give his methods a try and, more importantly, to help him procure the right corpse.⁴⁵

On January 17, 1802, Aldini acquired the body of George Forster, a young and healthy man who was hanged

after being convicted of murdering his wife and infant child. Aldini had arranged a demonstration ahead of the hanging, and many of London's highest medical and social society were in attendance. After the hanging, Forster's body was kept at an outside temperature of 30°F for several hours before its delivery to Aldini. Using a voltaic pile to apply electricity, Aldini skillfully began the exhibition by applying the electrodes to the head, causing the eyes to open, the jaw to move, and the face to contort in various expressions of pain. He then moved the electrodes such that the head moved from side to side as though looking at the crowd. Further demonstration included the raising of a clenched fist and setting the legs in motion, and for the finale, Aldini cracked open Forster's chest and attempted to restart the heart. The heart quivered, but to Aldini's disappointment, Forster remained dead. The effect on the

In 1791, French physician Philippe Pinel, best known

theme of cold versus warmth and transitions between the two. These transitions serve as a running metaphor throughout the story of a creature that is neither living nor dead, but rather stuck in a suspended state of animation. This suspended state is precisely what Hunter intended to study when he began freezing fish: life forms caught somewhere between life and death. Shelley's story is narrated by the captain of a ship searching for passage through the northern ice cap, struggling with his crew against the brutal cold. Frankenstein's monster, the embodiment of the life-and-death dichotomy, remarks upon seeing his first changing of the seasons, "I was better fitted by my conformation for the endurance of cold than heat."^{45,62} In the final scenes of the book, Frankenstein pursues the monster to the frigid North Pole, where en route, he is stranded on an iceberg and rescued by the story's narrator. The monster himself perishes after lighting himself on fire once he reaches the North Pole. Shelley's novel is revealing not only of her era's infatuation with discovering the principle of life, but also of a growing philosophical understanding of death and life, cold and warmth, and the suspended state of animation that is achieved via hypothermia.^{45,62}

Hypothermia in the 19th and Early 20th Centuries

In 1791, French physician Philippe Pinel, best known

FIG. 6. A painting by Tony Robert-Fleury showing Pinel unchaining women in a Parisian asylum in 1795 (painted in 1875). Figure is in the public domain.

for his leading role in the development of humane treatment strategies for patients with psychiatric disorders (Fig. 6), reported on the interesting case of a young man with mania who escaped the asylum and spent a hypothermic night wandering naked through the wintry surrounding forest. Upon his recovery and rewarming, he was reportedly cured of his mania.⁵² Accordingly, hypothermia was used extensively to treat all kinds of mental illness during the 19th century because of lasting belief in the Hippocratic theory that, if disease was caused by or produced excess heat, then mental illness must be a disease of excess heat in the brain. Methods for inducing hypothermia included cold-water immersion, swinging the person in a hammock while drenching him or her with cold water (the motion of the hammock was meant to promote evaporation), and applying ice packs to shaved heads.

Beliefs in the curative properties of hypothermia for mental illness persisted into the early 20th century. They were actively investigated by John Talbott, a physician who worked at the McLean Hospital for the Insane in Belmont, Massachusetts. He cited the promising effect of plunging insane patients into cold water as precedent for his experiments with schizophrenia. In 1941, he published a report of his experience with 10 schizophrenic patients, for whom standard therapy with insulin and pentylene-tetrazol (a convulsant) had failed.^{69–71} Each patient was sedated with a barbiturate and then kept at a body temperature of near 80°F for up to 68 consecutive hours. Four of the 10 patients had a positive and enduring effect, 3 of the patients had a positive but temporary effect, 2 of the patients had no effect, and 1 patient died of circulatory collapse upon rewarming. Numerous concurrent and subsequent attempts failed to reproduce the same benefit, but many reproduced the often-fatal side effects. Hypothermia was

thus never widely accepted in the 20th century as an appropriate treatment modality for mental illness.¹⁹

Modern History

Temple Fay

Temple Fay, the head of the Neurosurgery Department at Philadelphia's Temple University Hospital in the 1930s, is credited by many as having introduced hypothermia, both whole-body and localized, to modern-day medical practice (Fig. 7). His interest in hypothermia as a therapeutic measure began in 1919, when as a sophomore in medical school he was asked by a professor why cancerous metastases were seldom found below the knees and elbows. Fay answered that he did not know, and his examiner admitted that he did not know either. This experience greatly impressed his young mind and eventually led him to the work he is most known for today: the effects of low body temperature on cellular growth and on cancer in particular.

Before introducing hypothermia to the modern medical era through his groundbreaking clinical trials at Temple University, Fay conducted a complete and systematic course of laboratory investigations that provided the foundation for future research into the mechanism of neuroprotection via hypothermia.^{22,32} By the early 20th century, much had been published on the effectiveness of hypothermia as a tissue preservative, and a handful of early pioneers reported favorable responses to hypothermia for various conditions, including tumor growth, inflammation, and pain.³² Despite these early clues, no one before Fay is known to have taken the logical next step of investigating the effects of hypothermia on tissue culture growth in the laboratory.

FIG. 7. Temple Fay (January 9, 1895–August 19, 1963) in 1940 at the time of his most intense activity in hypothermia research. Publicly, Fay was perhaps more notorious for his support of the Doman-Delacato “patterning” treatment. Photograph courtesy of Special Collections Research Center, Temple University Libraries, Philadelphia, PA.

Having observed that cancerous metastases are more frequently found in those areas of the body with the highest temperature, Fay’s next step was to study the direct effects of hypothermia on living cells. At his family’s chicken farm in Maryland, he studied chick embryo development at both normal and hypothermic temperatures. He discovered that hypothermia produced a marked inhibition of embryonic growth, with nearly complete cessation of cellular differentiation at 32.2°F. Discovering the teratogenicity of hypothermia to embryonic chick cells was a critical finding; if normal undifferentiated cells require a normal temperature to continue dividing, perhaps undifferentiated cancer cells did, too. His logical next step was to investigate the growth of both normal and cancerous cells at varying temperatures. He found that healthy, differentiated cells exhibited much greater cold tolerance than malignant, undifferentiated cells.^{22,23}

Fay began by studying the temperature in various sites of the body, and discovered that temperatures below the elbows and knees diminished as much as 12°F to 20°F from the central temperature. This finding prompted a series of laboratory studies on the effects of cold on tissue cultures and chick embryos. He discovered that cellular differentiation ceased almost completely at 90°F. By 1938, armed with this critical information, Fay felt confident enough in the therapeutic potential of hypothermia to take his work from the bench to the bedside.^{22,23} Courageously,

and almost entirely alone among his doubtful and critical colleagues, Fay began the largest series of human hypothermia experiments of its time, a series of experiments that would go on to launch the field of hypothermia into the mainstream of modern-era neurosurgery.

But first, Fay needed to invent a new clinical thermometer that was calibrated below 94°F. Survival below 94°F had been believed impossible, the so-called thermal barrier; thus, there were no clinical thermometers available that were calibrated below that temperature. Between 1938 and 1940, he carefully planned and conducted the reduction of 126 patients’ whole-body temperature on 169 experiments, first to levels around 90°F to 92°F, then eventually as far down as 75°F. These studies demonstrated that whole-body refrigeration was survivable to temperatures well below 94°F.

Fay’s first hypothermia patient was a young woman with metastatic breast cancer and debilitating pain, who was admitted to Fay’s neurosurgical service for consideration of cordotomy as a means of relieving her pain. He began by applying cold locally to a fungating breast tumor constantly for several weeks. Repeat biopsies showed regressive effects on the tumor cells, and the local infection was noted to have cleared as well (highly noteworthy considering this was in the days before antibiotics). He also noted a remarkable response in wound healing, with microscopic clearance of local tumor growth confirmed on further biopsies. Encouraged by this result and concerned by her persistent systemic pain from widespread metastases, he decided to reduce her entire body temperature. In November the patient was put in a closed room of the hospital with the heat off, windows open, and her body surrounded in 150 lb of cracked ice. Under tribromoethanol anesthesia, by late afternoon she had a rectal temperature in the low 90s. Fay carefully monitored her respiratory status and nearly pulseless bradycardia. Eighteen hours later, she was rewarmed and reported reduced pain. He reported a reduction of pain symptoms in 95.7% of surviving patients and a mortality rate of approximately 10%, a number he felt comfortable with considering that he told patients that the odds of survival were 8:1 when he obtained consent. His patients were all considered to have only weeks remaining to live, and many of those surviving patients went on not only to have a better quality of life, but also to live longer than otherwise predicted.

Despite his early success, Fay’s work was nearly lost to a mutiny among the nursing staff, who believed that service on Fay’s “cold ward” was too demanding because the physical conditions were arduous and the nurses were constantly worrying about the weak respirations of patients, their seemingly absent pulse, the difficulty in obtaining a blood pressure reading, and the inability to obtain a body temperature using standard hospital thermometers. In response, Fay developed special blankets (in cooperation with the Therm-O-Rite Co.) that could be wrapped around the patient; these had various cold solutions pumped through them using beer-cooler machine pumps. He also worked to develop new rectal thermometers that could continuously and accurately record body temperatures far below normal.

Soon after his experiments with whole-body refrigera-

FIG. 8. Schutzstaffel (SS) doctors at Dachau conducting the immersion-hypothermia experiments in 1942. Sigmund Rascher appears in the front in the left photograph. Note the ice chunks in the tub of water. After the conclusion of the official study, Rascher was apparently involved in the murders of more prisoners to enhance his contribution for a scientific conference and to expand his later postdoctoral thesis with the additional autopsy findings. "I take the liberty to enclose the final report on the hypothermia experiments in Dachau.... Also not included in this report is the microscopic pathological examination of the brain stem of the deceased.... Till the conference I will conduct more experiments and hope to be able to present further results in this period." [Rascher S: Final report from Dr. Sigmund Rascher sent to Heinrich Himmler, Oct. 16, 1942, Staatsarchiv Nürnberg, Germany]. Himmler replied to Rascher: "I view those people who today still reject these human experiments, preferring instead to let courageous German soldiers...die, as guilty of high treason and as traitors..." [Himmler H: Letter to Sigmund Rascher, Oct. 24, 1942, Staatsarchiv Nürnberg, Germany]. The German military leadership was unable to influence or take control of the project. Rascher and his wife, Karoline, who was 16 years older than Rascher and who also promoted his career along with Himmler, came to ironic deaths. After learning that they had committed fraud with regard to the false reporting of births when instead they had kidnapped their 4 "Aryan" children, the deceived Himmler exacted the ultimate revenge. Rascher's wife was sent to the Ravensbrück concentration camp and executed in 1945, while Rascher was sent to the Buchenwald concentration camp and then transferred to Dachau in April 1945, where he was executed. Used with permission from Bildarchiv Preussischer Kulturbesitz. Rights provided by US-based partner, Joyce Faust, Permissions Associate, Art Resource, Inc. www.artres.com.

tion, Fay began studying localized cryotherapy as treatment for brain lesions. He developed small metal capsules that housed a circulating refrigerant (which he referred to as cold "bombs") and implanted these capsules into the human brain as a local treatment for abscess, cerebritis, cancer, and osteomyelitis. In cases of open surgery for brain abscess and cerebritis, he oftentimes directly irrigated refrigerated saline and boric acid into the active area of infection. He noted satisfactory responses for both infectious and neoplastic disease processes. He was most inspired by 123 results in the surrounding tissue margin that showed degenerative changes in the affected tissues and a striking lack of inflammation or infection around the capsules, which were sometimes left in place for weeks. He also experimented with whole-head cooling in cases of trauma, and he developed a head wrap specifically for this purpose.^{22,32}

Fay worked closely with his pathology colleagues at Temple University during his years of generalized and localized cooling experiments on humans. Repetitive biopsies and autopsies of his patients provided the first evidence that hypothermia arrests human malignant cellular growth and metabolism. Fay found that hypothermia is bacteriostatic, reduces inflammation and edema, and, when applied locally to cutaneous cancer metastases, produces a marked tendency toward tumor regression, infection clearance, and slow healing, with subsequently more pliable scars (greatly reduced contractures). Fay extended his research into the physiological effects of hypothermia. He examined biopsy and postmortem tissue, which led him to discover that hypothermia results in better utilization of oxygen by the brain after traumatic injury and that a rise

in cerebrospinal fluid volume and a decrease in intracranial blood volume may explain the bradycardia, depressed respirations, and elevated blood pressure associated with hypothermia. These and numerous other laboratory and clinical discoveries led Fay to develop the first deliberate program of hypothermia for traumatic brain injury (TBI). He reasoned that TBI is a clinical condition that would benefit greatly from decreased intracranial pressure and improved utilization of oxygen by cerebral tissue.^{22,32}

World War II Dachau Immersion-Hypothermia Experiments

Despite the accumulation of promising clinical data on his patients' response to hypothermia as treatment for pain, infection, and cancer, Fay believed that his work did not receive appropriate acknowledgment.³² One group of scientists who took a keen interest in his results was at the Dachau concentration camp. In 1940, the Germans obtained a copy of Fay's manuscript detailing his experience with hypothermia. For the proposed purpose of searching for new ways to help German airmen survive when shot down and stranded in the cold open North Sea, Nazi scientists used concentration camp prisoners in a series of infamous hypothermia experiments that were conducted oftentimes with an intentional end point of death.⁸ A relatively immediate postwar report by Alexander and a subsequent analysis by Berger have detailed the project.⁸

The Nazi immersion-hypothermia project consisted of around 400 experiments carried out on about 300 prisoners from August 1942 to May 1943 at Dachau (Fig. 8). The project was proposed by Air Force Field Marshal Erhard Milch and became the special interest of Reichsführer Heinrich

Himmler, who believed himself to be an expert medical scientist, and who directed or approved all such experimentation. Himmler traveled several times to Dachau to personally observe experiments conducted under the supervision of Professor Ernst Holzlöhner, Dr. Sigmund Rascher, and Dr. Erich Finke. Forging a close and odd relationship with Himmler, the obsequious and sycophantic Rascher consequently received full support from Himmler for various studies on Dachau concentration camp prisoners.

During postwar testimony, assistants stated that at least 80–90 prisoners died of the hypothermia experiments, whereas only 2 prisoners were known to have survived the war, and both were “mental cases.” Subjects of the experiments were male prisoners of the Dachau complex, many of whom were Russian prisoners of war. Neurological effects of the cooling were of central interest. Rascher recorded:

The experimental subjects were placed in the [tub filled with icy] water, dressed in complete flying uniform, winter or summer combination, and with an aviator's helmet. A life jacket made out of rubber kapok was to prevent submerging. The experiments were carried out at water temperatures varying from 2.5 to 12 Centigrade. In one experimental series, the occiput (brain stem) protruded above the water, while in another series of experiments the occiput (brain stem) and back of the head were submerged in water. Electrical measurements gave low temperature readings of 26.4 in the stomach and 26.5 in the rectum. Fatalities occurred only when the brain stem and the back of the head were also chilled. Autopsies of such fatal cases always revealed large amounts of free blood, up to one-half liter, in the cranial cavity.⁴⁷

The prisoners were connected to measuring instruments and were in various states of clothing, with immersion testing usually lasting hours. Some experiments were carried out with the prisoners under anesthesia or heavy sedation:

If the experimental subject was placed in the water under narcosis, one observed a certain arousing effect. The subject began to groan and made some defensive movements. In a few cases a state of excitation developed. This was especially severe in the cooling of head and neck. But never was a complete cessation of the narcosis observed. The defensive movements ceased after about 5 minutes. There followed a progressive rigor, which developed especially strongly in the arm musculature; the arms were strongly flexed and pressed to the body. The rigor increased with the continuation of the cooling, now and then interrupted by tonic-clonic twitchings. With still more marked sinking of the body temperature it suddenly ceased. These cases ended fatally, without any successful results from resuscitation efforts.⁴⁹

Incredible efforts were made to set up, justify, and report the experiments, especially by the enthusiastic Rascher, who wrote in October 1942:

The Reich leader SS wants to be informed of the state of the experiments. I can announce that the experiments have been concluded, with the exception of those on warming with body heat. The final report will be ready in about 5 days. Prof. Holzlöhner, for reasons I cannot fathom, does not himself want to make the report to the Reich Leader Himmler and has asked me to attend to it. This report must be made before 20 October, because the great Luftwaffe conference on freezing takes place in Nürnberg on 25 October. The report on the results of our research must be made there, to assure that they

be used in time for the troops. May I ask you to arrange for a decision from the Reich Leader regarding the final report to him, and the submission to him of the relevant material? Today I received your letter of 22 September 1942, in which the Reich Leader orders that the experiments on warming through body heat must absolutely be conducted. Because of incomplete address it was delayed. Today I asked Obersturmbannführer Sievers to send a telegram to the camp commander immediately, to the effect that four Gypsy women be procured at once from another camp.⁴⁸

The reports Rascher mentions in the quotation above were made under the titles “Prevention and Treatment of Freezing” and “Warming Up After Freezing to the Danger Point.”⁵⁵

As the horrors of Nazi medical experimentation in immersion hypothermia at Dachau became known, legitimate undertakings of hypothermia research suffered a severe setback. As for Fay, he discontinued his clinical and research programs on hypothermia following these events. In 1944 he wrote:

The wide application of cold therapy almost 100 years ago, when ice was a luxury, reflects today that ever human tendency to ignore what is plentiful, common, and easily at hand. The field of refrigeration or hypothermy is broad and deep, awaiting exploration by those who have modern facilities....²²

Rediscovery in the 1950s–1960s

As the stigma of the Dachau hypothermia experiments began to wear off, animal and human investigations resumed. With the rejuvenation of interest in hypothermia research after World War II, Crossman and Allen¹⁷ reported in 1946 that as the body temperature decreases, more oxygen remains in solution in the blood, tissues, and cells themselves. The net result is a reduced cellular metabolism and a reduced need for oxygen delivery. In 1954, Rosomoff and Holaday⁵⁸ published the findings of their laboratory investigations on cerebral metabolism in the hypothermic state. Using a canine model, they showed that hypothermia induced a marked decrease in cerebral metabolism, a decrease in cerebral blood flow and brain volume, and a more rapid transition from the exudative to the reparative stages of injury.

The “younger” neurosurgeons who took up the work of Fay included Lougheed, Botterell, Sweet, and Vandewater and their coworkers.^{10,11,22,44,73} Citing the success of Bigelow and his colleagues with improving outcomes for open cardiac surgery with generalized hypothermia, Lougheed, Botterell, and others began treating numerous types of cerebrovascular lesions while the patients were under hypothermic cerebrovascular arrest. Between 1955 and 1958, these surgeons accrued a case series of 100 consecutive patients, 83 with saccular intracranial aneurysms, who underwent induced hypothermia intraoperatively, although with promising but inconclusive results. In the early 1960s, other teams of cardiac surgeons and neurosurgeons used extracorporeal circulation and hypothermia during aneurysm surgery.²⁰

While these surgical pioneers were pushing the limits of hypothermic cerebrovascular arrest, neurosurgeon-scientist Robert White (Fig. 9) was establishing the famous Brain Research Laboratory (BRL) at Western Reserve

University, a single research center that would become the most productive center for hypothermia research in the modern era (as a Case Western Reserve University laboratory). The BRL existed from 1961 until 1996, and throughout its existence, the major theme of its work was hypothermia and its effects on the central nervous system. White and his team developed the first totally isolated brain preparations and transplantations, which provided numerous opportunities to investigate brain metabolism, neurophysiology, immunology, and rheology in normothermic and graded hypothermic states. In 1970, using their tenets of hypothermia and neuroprotection, White and his team successfully transplanted a primate head onto a recipient primate body. The animal regained consciousness and had appropriate cranial nerve responses to various stimuli but was quadriplegic. In the final days of the BRL, White was still pursuing his interest in cerebral hypothermia as he attempted to supercool the brain (-40°C or lower) using special perfusates that avoided cellular destruction via ice crystal formation.⁷³

During the time that White led his team in studying head transplants in primates, he was invited to Moscow to examine Vladimir Lenin's preserved brain, consulted with Boris Yelstin's doctors, and he assisted the physicians treating the gunshot wounds of Pope John Paul II in Rome. He was a controversial champion of animal experimentation and withstood numerous protests of his work. His family endured frequent phone calls to their home asking for "Dr. Butcher," and a banquet in his honor was interrupted by a protester who offered him a bloody replica of a human head. When he testified in a civil hearing on the Sam Sheppard murder case, a lawyer compared him to Dr. Frankenstein. Although the intention was certainly to insult White and his work, this comparison is ironic considering that Dr. Frankenstein's character may have been inspired by a man obsessed with discovering what animates the physical body (Aldini), whereas White seems to have devoted his life's work, in his own words, to discovering what animates "the physical repository for the human soul [the brain]."^{61,75}

White's tissue preservation work was ahead of its time, as noted by his comments in various opinion pieces: "We have to acknowledge the probability that eventually all the major cellular complexes of the human body will be replaceable either by transplanted organs (man or animal) or by sophisticated engineering modules."⁷⁸ Taken to its logical end, this argument implied that "like all biological activity, life and death merge into one another representing a continuum and the neuro-scientist can only in the final analysis determine the point of irreversibility of this highly complex system at which the possibility of organized activity that characterizes behavior has been exceeded."⁷⁸

Intraoperative Hypothermia for Neuroprotection: Lost Interest in the 1970s, Resurgence in the 1980s, and Narrowing of Indications in the 21st Century

Although early experiments with hypothermic anesthesia and treatment of trauma were promising, the 1970s saw the publication of numerous studies demonstrating high complication rates of prolonged severe hypothermia (presumably attributable to cold-induced coagulopathies)

FIG. 9. Robert J. White (January 21, 1926–September 16, 2010), a neurosurgeon and scientist at Case Western Reserve University, who carried out a series of studies of hypothermia and undertook full head transplant experiments on animals. From the archives of The Metro-Health System, Cleveland, Ohio. Used with permission.

as well as numerous animal studies showing worsened survival in various neurological disease states.^{66,67} As evidence mounted that the risk-to-benefit ratio for induced hypothermia did not favor treatment, clinicians began to lose interest in therapeutic hypothermia.

However, with the 1980s came improvements in the management of preoperative coagulopathies as well as in microsurgical techniques. By the late 1980s, several cerebrovascular centers had resumed the practice of hypothermic neuroprotection during surgery employing cardiac standstill. Silverberg and Baumgartner and their colleagues^{7,64} were among the earliest to revisit this technique for patients undergoing repair of otherwise inoperable neurovascular lesions. With their promising results, and the help of numerous animal studies exploring graded depths of hypothermia and increasing lengths of cerebrovascular arrest, interest continued to grow.

In 1985, Spetzler and his cerebrovascular team at Barrow Neurological Institute began what would eventually become the largest single-institution experience with deep intraoperative hypothermia and cardiac arrest for cerebral aneurysm surgery. Between 1985 and 2009, with most cases in the mid-1990s, a total of 105 patients with complex cerebrovascular lesions were treated with intraop-

FIG. 10. Intraoperative photograph taken during hypothermic cardiac arrest at Barrow Neurological Institute, 1986, showing the operating neurosurgeon Robert F. Spetzler explaining details of the surgery to journalists. Copyright Barrow Neurological Institute. Used with permission.

erative hypothermia and cardiac arrest (Fig. 10). As the Barrow experience with intraoperative hypothermia grew, the indications for its use began to narrow. Over time, this technique became reserved for the treatment of giant and complex posterior circulation aneurysms, particularly those at the basilar apex. As alternative microsurgical and endovascular techniques for the treatment of these complex aneurysms evolved, cardiac standstill became obsolete. Between 2004 and 2009, only 6 cardiac standstills were performed at Barrow Neurological Institute. None have been performed since 2009.^{42,53–56,65,82}

In the 1990s, mild hypothermia was shown not only to be beneficial for severe TBI and intracranial hypertension but also to be associated with fewer coagulopathies and other systemic side effects in comparison with deeper hypothermia.⁶³ By the early 2000s, randomized control trials showed reduced morbidity and mortality and improved neurological outcomes among patients with anoxic brain injury treated with hypothermia after out-of-hospital cardiac arrest.^{9,35} These studies secured a permanent place for hypothermia in the postresuscitation treatment guidelines⁵¹ and reinvigorated basic hypothermia research and numerous clinical trials of hypothermia.

With regard to spinal cord injury (SCI), van Harreveld and Tyler⁷² first reported the beneficial effects of hypothermia after SCI in 1944. They demonstrated that hypothermia reduced tissue damage and resulted in better functional outcomes in animals with induced SCI that were treated with systemic hypothermia at 28°C. This work was continued at BRL by White and his colleagues, especially Albin, an anesthesiologist who used a canine model of graded experimental SCI and a novel subarachnoid perfusion device to provide rapid, continuous, and deep hypothermia to the spinal cord. Data from these studies demonstrated the early salutary effect of localized cooling after experimental injury. These studies formed the basis for experimental trials of subarachnoid cooling in humans after accidental SCI.⁷⁵

Just as interest in the treatment of brain disorders with cooling waned in the 1970s, so did interest in spinal cord cooling. However, the resurgence of interest in the early 1980s led to experimentation with hypothermia in patients

undergoing abdominal aortic aneurysm repair. The earliest reports of the protective role of hypothermia for the spinal cord in patients with aortic aneurysms were published in the mid to late 1960s.³⁸ Nonetheless, it was only beginning in the 1980s that laboratory and clinical studies of several cooling techniques were conducted on this topic, resulting in advanced techniques 20 years later, such as the first experiments to successfully cool selective brain regions via an endovascular intra-arterial procedure.^{15,16,27,28,39,41} The applications of hypothermic intervention set the stage for later studies into the various triggers of cellular and molecular neurotoxic cascades.^{30,40}

Conclusions

The history of therapeutic hypothermia in neurosurgery is fascinating not only for its cast of colorful characters and miraculous accounts of survival and recovery but also for its reflection of our profession's commitment to the process of scientific inquiry and bench-to-bedside research. Although the therapeutic benefits of cooling have been known for at least 5000 years, investigations into hypothermia have also been associated with notorious, horrific, and unscientific human experimentation. Unfortunately, much of the latter has taken place during the modern era and has been disruptive to what might otherwise have been progressive experimentation yielding productive and clinically useful results. Within each era of medical advancement since Imhotep's first description of localized cooling, pioneer physicians have steadfastly pursued the ability to prevent or rescue neurological morbidity using "what is plentiful, common, and easily at hand."²² Despite centuries of anecdotal, laboratory, and animal studies showing extremely promising benefits of hypothermia in treating numerous disease processes, human clinical trials from the past 50 years have largely failed to show a convincing benefit of hypothermia over controlled normothermia. Although our commitment to practicing evidence-based medicine has appropriately kept hypothermia out of the current neurosurgical standards of care, our commitment to finding better ways to prevent neurological morbidity and to influence neural function should keep our interest in hypothermia research alive.

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Disclosures

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Author Contributions

Conception and design: Preul, Bohl, Zabramski, Spetzler. Acquisition of data: Preul, Bohl, Martirosyan, Killeen, Belykh. Analysis and interpretation of data: all authors. Drafting the article: Preul, Bohl, Martirosyan, Killeen, Belykh. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Administrative/technical/material support: Preul, Bohl. Study supervision: Preul, Zabramski, Spetzler.

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