Perioperative Fluid Management

Ehab Farag
Andrea Kurz
Christopher Troianos
Editors

Second Edition

Springer

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To the memory of my mom, Evangeline Troianos, and my father Achilles Troianos, to my wife Barb for her timeless love and unwavering support, and to my children and their spouses: Rachael, Andrew and Allison Troianos, and Rebecca Troianos and Justin Morris Christopher A. Troianos.

My sincerest thanks to my parents Mrs. Suzan Roufael and the late Mr. Samir Farag, to my wonderful wife Abeer, and to my dearest daughters Monica and Rebecca for their constant support, love, and encouragement.

Ehab Farag

Foreword

I have the honor of serving Cleveland Clinic alongside 66,000 caregivers. We share the vision to become the best place to receive care anywhere and the best place to work in healthcare. In the course of my work as a cardiac surgeon and CEO, I have the privilege of interacting with colleagues from a wide variety of backgrounds and professional interests.

Dr. Ehab Farag, Dr. Andrea Kurz, and Dr. Christopher Troianos with the Cleveland Clinic are the coeditors of *Perioperative Fluid Management*, *Second Edition*. Working with a renowned team of international contributors, they have developed a comprehensive study of perioperative fluid management. Their team is comprised of highly accomplished anesthesiologists, intensivists, and surgeons from the United States and Europe.

The team has explored perioperative fluid management in depth, ranging from the history of intravenous fluid to the recent and exciting opportunities to employ artificial intelligence. The book has clinical scenarios for almost every case in clinical practice. Their work is a testament to the importance of research, collaboration, and the need for continued innovation in healthcare. I believe their groundbreaking analysis will lead to improved patient care and foster further innovation.

I am pleased to recognize the importance of this work and to recommend *Perioperative Fluid Management*, *Second Edition*, to all the committed caregivers who work in the critically important field of fluid management.

Tomislav Mihaljevic
Cleveland Clinic
Cleveland, OH, USA

Preface for the Second Edition

Fluid management is still one of the most debated subjects in perioperative medicine. There are a lot of misconceptions and unsettled issues in perioperative fluid management. In the second edition of *Perioperative Fluid Management*, our motto is to present the most advanced evidence-based science in fluid management. Moreover, we tried our best not to leave a stone unturned in fluid management. In this edition, most of the chapters have been updated and revised from the first edition. The chapters on "Endothelial Glycocalyx and Revised Starling Principle" by Drs. Curry and Michel, the fathers of modern microcirculation, are of special recognition in this updated edition. We have added new chapters on the use of venous circulation in fluid management, the use of albumin in intensive care, and the use of dynamic arterial elastance in goal-directed fluid therapy. In addition, we have added new case scenarios in pediatric, obstetric, and intensive care patients to help clinicians have a strong armamentarium of fluid management strategies in every clinical scenario. We would like this edition, as was our intent for the previous edition, to be of benefit to all perioperative physicians in guiding fluid management.

Finally, we would like to express our gratitude to our colleagues who authored the book chapters and for their dedication to advancing the field. We would also like to thank the Springer publishing team for all their help and support during the publishing process of this book.

Editors

Cleveland, OH	Ehab Farag
Cleveland, OH	Andrea Kurz
Cleveland, OH	Christopher Troianos

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Part I

Fundamentals of Fluid Management

A History of Fluid Management

1

Elizabeth A. M. Frost

Abstract

A history of fluid management is discussed focusing on the following key points: Bloodletting has been performed for more than 2000 years and is still used today, albeit for different reasons. While bloodletting was ordered by physicians, it was usually carried out by barber surgeons, thus dividing the two. Circulation of blood was not appreciated until William Harvey in the first century, and it was not immediately accepted as it was contrary to the teachings of Galen and others. The concept of the need for fluid replacement rather than bloodletting grew out of the worldwide cholera epidemic of the nineteenth century. Only over the past 60 years have fluids routinely been given intraoperatively.

Key Points

1. Bloodletting has been performed for more than 2000 years and is still used today, albeit for different reasons.
2. While bloodletting was ordered by physicians, it was usually carried out by barber surgeons, thus dividing the two.
3. Circulation of blood was not appreciated until William Harvey in the first century, and it was not immediately accepted as it was contrary to the teachings of Galen and others.
4. The concept of the need for fluid replacement rather than bloodletting grew out of the worldwide cholera epidemic of the nineteenth century.
5. Only over the past 60 years have fluids routinely been given intraoperatively.

The life of the flesh is the blood (*Leviticus* 17:11–14)
Take drink…this is my blood which is shed for you for the remission of sins (*Matthew* 26)

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Earliest Times

Long before biblical times, blood and body fluids were believed to have magical powers. Blood was the cornerstone of life and regarded as a gift. Hence, it was often used in sacrificial offerings to appease the gods. The Sumerians of Mesopotamia (4th–2nd millennium BCE) considered the vascular liver as the center of life [1, 2]. The priests of Babylon taught that there were two types of blood: bright red day blood in the arteries and dark night blood in the veins. In the *Yellow Emperor's Classic of Internal Medicine*, the *Nei Ching Su Wen*, an ancient Chinese text compiled about 4500 BCE, the heart and pulse were connected and all the blood was said to be under the control of the heart and flowed continually until death (Fig. 1.1) [3].

Egyptian physicians were aware of the existence of the pulse and also of a connection between the pulse and heart. The Smith Papyrus, ascribed by some to Imhotep who lived around 2650 BCE and was the chief official of the Pharaoh Dosier, offered some idea of a cardiac system, although perhaps not of blood circulation (Fig. 1.2) [4]. Distinction between blood vessels, tendons, and nerves was not

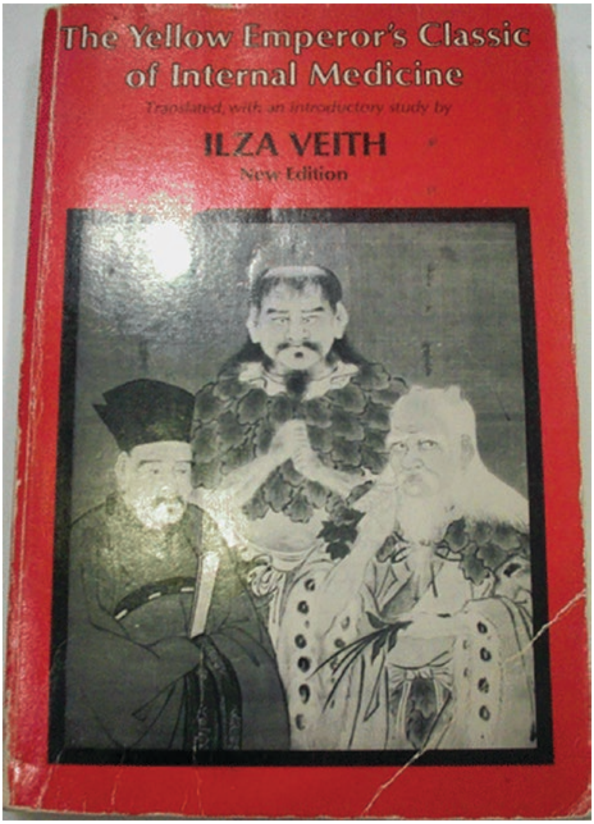

Fig. 1.1 The Yellow Emperor's classic of internal medicine. On page 34, one reads, "When people lie down to rest, the blood flows back to the liver"

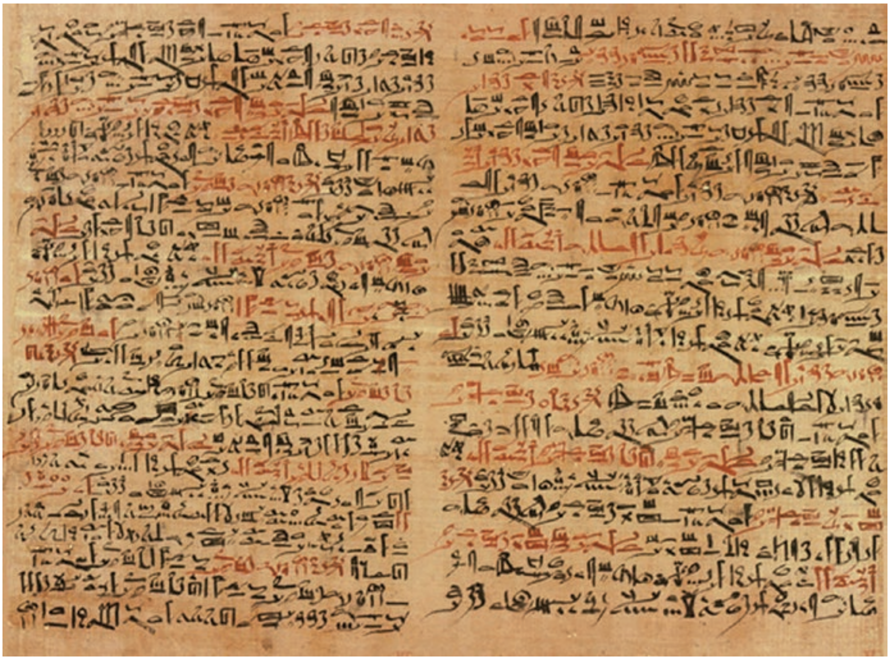

Fig. 1.2 The Edwin Smith Papyrus. The original is housed in the New York Academy of Medicine, NY, NY

made. A theory of "channels" that carried air, water, and blood to the body was analogous to the River Nile; if the river became blocked, crops were unhealthy. This principle was applied to the body: If a person was unwell, laxatives should be used to unblock the "channels."

Greek philosophers began investigations into the circulation also in the second millenium BCE. Aristotle, a physician of the fourth century BCE, believed that blood was manufactured in the heart and then distributed to other tissues [1]. Erasistratus, an anatomist of the third century BCE, is credited for his description of the valves of the heart. He also concluded that the heart was not the center of sensations, but instead functioned as a pump [5, 6]. He distinguished between veins and arteries but believed that the arteries were full of air and that they carried the "animal spirit" (*pneuma*). But Galen, in the second century CE, disagreed with Erasisratus, believing that blood was made in the liver and that it moved back and forth until it was consumed [7]. This theory remained unchallenged until 1628 when William Harvey published his treatise, *De Motu Cordis* [8].

Between the first and sixth centuries CE, consumption of the blood of Roman gladiators was said to cure epilepsy [9]. After the banning of gladiatorial fighting around 400 CE, it became the practice to drink the blood of executed prisoners, especially if they were beheaded. Epileptic patients were described as crowding around the scaffold, cups in hand, waiting to "quaff the red blood as it flows from the still quavering body of a freshly executed criminal" [10]. There are some reports that this supposed cure for the "falling sickness" existed until the nineteenth century [9].

Consuming blood was also thought to restore youth. A fifteenth-century physician noted: "There is a common and ancient opinion that certain prophetic women who are popularly called 'screech-owls' suck the blood of infants as a means, insofar as they can, of growing young again. Why shouldn't our old people, namely those who have no [other] recourse, likewise suck the blood of a youth?—a youth, I say who is willing, healthy, happy and temperate, whose blood is of the best but perhaps too abundant. They will suck, therefore, like leeches, an ounce or two from a scarcely-opened vein of the left arm; they will immediately take an equal amount of sugar and wine; they will do this when hungry and thirsty and when the moon is waxing. If they have difficulty digesting raw blood, let it first be cooked together with sugar; or let it be mixed with sugar and moderately distilled over hot water and then drunk" [11].

Suggested as perhaps the first attempt at blood transfusion, three young boys were bled and the blood given to Pope Innocent VIII by his Jewish physician Giancomo di San Genesio in 1492 [1, 2]. It is, however, more likely that the pope drank the blood. Nevertheless, the boys and the pope all died and the physician disappeared. It is also possible that the story was circulated as an anti-Semitic campaign as the pope was very ill at the time.

Contrary to the idea of blood consumption was that propagated by the teachings of Charles Taze Russell, founder of the Bible Student Movement. He started publishing Zion's Watch Tower and Herald of Christ's Presence in 1879. In 1881 he founded Zion's Watch Tower Tract Society, later the Jehovah's Witness sect. Based on quotations from the Bible, members must abstain from eating blood, also interpreted as, receiving blood transfusions (Acts 15: 20,29, Genesis 9: 3–5, Deuteronomy 15: 14–23, Leviticus 7: 26, 27).

Bloodletting

Bloodletting derived from a belief that proper balance to maintain health was required between the four humors—blood, phlegm, black bile, and yellow bile—based in turn on the Greek philosophy of the elements of water, air, fire, and earth [12, 13]. Galen felt that blood was the dominant humor and the one most to be regulated. To balance the humors required removal of blood or purging. Aretaeus of Cappadocia, probably a first-century CE contemporary of Galen, advocated venesection for the treatment of "phrenetics": "If the delirium and fever have come on in the first or second day it will be proper to open a vein at the elbow, especially the middle" [14].

Bloodletting was the most frequently performed medical practice for more than 2000 years (Fig. 1.3) [15]. While trepanning of the skull allowed evil spirits to be released from the head, bloodletting facilitated the removal of the demons that caused disease from other parts of the body. The Egyptians used the

Fig. 1.3 Iatros, an ancient Greek word for "physician," is depicted on this old Grecian vase, bleeding a patient. The Peytel Arybalos, 480–470 BC, Louvre, Dpt.des Antiquites Grecques/Romaines, Paris. Photographer: Marie-Lan Nguyen, 2011 (Reprinted under Creative Commons license. https://creativecommons.org/licenses/by/3.0/deed.en)

technique at least by 1000 BCE, followed by the Greeks and Romans [12, 13]. While teaching that many diseases were caused by an overabundance in the blood, Erasistratus advocated initial treatment with vomiting, starvation, and exercise [6]. Overabundance or plethora was recognized by headache, tiredness, seizures, and fever. The practice of bleeding may have derived from the belief that menstruation occurred to "scourge women of bad humors" as taught by Hippocrates and Galen. Moreover, premenstrual cramps and pain were often relieved when blood flowed [1, 7, 16].

Precise instructions dictated how much blood should be removed based on age, general health, the season, and the weather. Either arterial or venous blood was drained depending on the disease. Blood vessels were identified depending on which organ they drained. The more severe the illness, the greater amount of blood was to be removed. Different religions laid down specific rules as to appropriate days; for example, select saints' days in the Christian calendar. Specific days of the week were also identified in the Talmud. The Talmud recommended specific days of the week and of the month for bloodletting [17]. Bleeding charts aligned bodily bleeding sites with the planets. Bloodletting was even used to treat hemorrhage before surgery and during childbirth to prevent inflammation. The amount of blood estimated to be in a limb was removed prior to amputation of that limb.

George Washington, the first US president, died on December 14th 1799 after having 3.75 l of blood removed from his body within a 10-h period as treatment for *cynanche trachealis* by Drs. James Craik and Gustavus Brown (most likely the president was suffering from a peritonsillar abscess, that would better have been managed by tracheostomy, as recommended by Dr. Elisha C. Dick who was overruled by the other two physicians because they were unfamiliar with the technique.) [18, 19].

Bloodletting was usually ordered by physicians but carried out by barber surgeons, thus dividing physicians from surgeons. The red-and-white-striped barber's

Fig. 1.4 Bloodletting woodcut from *Officia M.T.C* Cicero, 1531 (Source: Wellcome Library, London. Wellcome Images. Reproduced under Creative Commons Attribution 4.0 International license. https://creativecommons.org/licenses/by/4.0/)

pole represented gauzes wrapped around a stick [13]. The practice was standard treatment for all ailments, both prophylactically and therapeutically and persisted into the twenty-first century (Figs. 1.4 and 1.5) [13, 20].

Pierre Alexander Louis, a French physician of the nineteenth century, disagreed that fevers were the result of inflammation of the organs and bloodletting was an effective treatment for pneumonia [21, 22]. He published a paper in 1828 (expanded in 1834 to a book-length treatise in the *American Journal of Medical Sciences* entitled "An essay on clinical instruction"), demonstrating the uselessness of bloodletting. He met with strong resistance by physicians who refused to wait for reviews to determine if current treatments worked or change their practices of centuries. Gradually Louis' "numerical method" added objectivity to how patients should be treated to improve outcomes. He used averages of groups of patients with the same illness to determine effectiveness of therapies and accounted for age, diet, severity of illness, and treatments other than bloodletting. He also wrote of "averages" and "populations" and thus began the concept of "statistical probability."

During the early nineteenth century, leeches became popular (Fig. 1.6a, b). "Leech collectors," usually women, would wade into infested ponds, their legs bare. The leeches would attach themselves and suck several times their body weight of blood and then fall off, to be collected and sold to physicians [23]. In the 1830s, England imported about six million leeches annually for bloodletting purposes from France. Initially a very inexpensive treatment, scarcity of the little worms drove the price up and the treatment became less popular [23].

Fig. 1.5 An old photo of bloodletting during the nineteenth century. From the collection of the Burns Archive, PD-US

Fig. 1.6 (**a**) An artistic representation of a woman who is self-treating with leeches from a jar (Source: van den Bossche G. *Historia medica, in qua libris IV. animalium natura, et eorum medica utilitas esacte & luculenter*. Brussels: Joannis Mommarti, 1639. US National Library of Medicine). (**b**) Leeches as they were purchased in a jar

Beginnings of Intravenous Therapy

In 1242, an Arabian physician, Ibn al Nafis, accurately described the circulation of the blood in man [24]. He wrote: “The blood from the right chamber of the heart must arrive at the left chamber but there is no direct pathway between them. The thick septum of the heart is not perforated and does not have visible pores or invisible pores as Galen thought. The blood from the right chamber must flow through the vena arteriosa to the lungs, spread its substances, be mingled there with air, pass through the arteria venosa to reach the left chamber of the heart and there form the vital spirit…” [24].

Nevertheless, credit for the discovery of the circulation is generally given to William Harvey. He concluded: “The blood is driven into a round by a circular motion and that it moves perpetually and hence does arise the action and function of the heart, which by pulsation it performs” [8].

Harvey first presented his thesis, *De Motu Cordis*, at the Lumleian lecture (a series started in 1582) of the Royal College of Physicians in 1616 [25]. His insights evolved over several years thereafter and were finally published in 1628 in Latin in a 72-page book in Frankfurt, probably because that venue was host to an annual book fair that would allow the work greater attention [8]. The treatise was not translated into English until 1653. Such views of the circulation were contrary to the teachings of Galen and thus Harvey’s work was not immediately appreciated. Indeed, his practice suffered considerably, but no doubt the dedication of the book to King Charles I, to whom he was personal physician, helped in the ultimate acceptance of his conclusions and set the stage for intravenous therapy and fluid administration. Harvey did not know of the capillary system, the discovery of which is later ascribed to Marcello Malpighi, but he did describe fetal circulation [24].

Andreas Libavius, a German alchemist, imagined how blood could be taken from the artery of a young man and infused into the artery of an old man to give the latter vitality. Although he described the technique quite accurately in 1615, there is no evidence that he actually transfused anyone [1, 24]. The same can be said for the Italian, Giovanni Colle da Belluno, who mentioned transfusion in 1628 in his writings on “methods of prolonging life” [24].

Perhaps the first person to conceive of transfusion on a practical basis was the Vicar of Kilmington, in England, the Rev. Francis Potter [26]. Described as a recluse eccentric, he was befriended by John Aubery, a close acquaintance of Harvey. Aubery an English antiquary and writer, recorded of Potter in 1649: “He then told me his notion of curing diseases by transfusion of bloud out of one man into another, and that the hint came into his head reflecting on Ovid’s story of Medea and Jason, and that this was a matter of ten years before that time” [27].

Potter used quills and tubes and attempted transfusion between chickens but with little success.

Francesco Folli, a Tuscan physician, claimed to be the originator of blood transfusion [28]. He was aware of Harvey’s work and felt it possible to cure all diseases and make the old young by transfusing blood. At the Court of the Medici he had given a “demonstration” of transfusion (it actually may only have been by diagrams) to Ferdinand II, Duke of Tuscany, who was not impressed and dismissed Folli. The latter went into seclusion and was unaware of the several advances by Richard Lower, Jean Baptists Denys, and others in the intervening years before he rushed to print a book, *Stadera Medica* (the Medical Steelyard, Florence, GF Cecchi, 1680), in which in a second section "Della Trasfusione del sangue" he asserted his claim as the inventor. He weighed the pros and cons of blood transfusion writing: "Discovered by Francesco Folli and now described and dedicated to His Serene Highness, Prince Francesco Maria of Tuscany." He postulated that 20 young men as donors could allow the patient to get fresh blood over a considerable time. He described his apparatus as a funnel connected by a tube from a goat's artery with a gold or silver cannula in the patient's arm [24]. Later he recanted and noted that it would be impertinent of him to give directions about an operation that he himself had never attempted [28].

Richard Lower, a Cornish physician, is credited as the first to perform a blood transfusion between animals (xenotransfusion) and from animals to man [29, 30]. Working with Christopher Wren, he performed a successful transfusion in 1665 by joining the artery of one dog to the vein of another by means of a hollow quill. Lower's major work, *Tractatus de Corde*, was published in 1669 and traced the circulation through the lungs, differentiating between arterial and venous blood. Believing that patients could be helped by infusion of fresh blood or removal of old blood, Lower transfused blood from a lamb to a mentally ill man, Arthur Coga, before the Royal Society on November 23, 1667. The procedure was recorded in Samuel Pepys' diary:

> …with Creed to a tavern and a good discourse among the rest of a man that is a little frantic that the College had hired for 20 shillings to have some blood of a sheep let into his body…I was pleased to see the person who had had his blood taken out…he finds himself better since but he is cracked a little in his head [2].

The same year, a French physician, Jean Baptists Denys, had administered the first fully documented human blood transfusion on June 15, 1667 [31, 32]. Using sheep blood, he transfused about half a pint into a 15-year-old boy, who had been bled with leeches 20 times (Fig. 1.7). Surprisingly, the boy recovered. Denys' second attempt at transfusion was also successful. However, his third patient, Baron Gustaf Bonde, died. Later in 1667, undeterred, Denys transfused calf's blood to Antoine Mauroy, who also died. Denys was accused by Mauroy's wife of murder. He was acquitted, and it was later found that the patient had died of arsenic poisoning. But considerable controversy arose and in 1670 blood transfusions were banned until the first part of the nineteenth century (around 1818) when James Blundell, using only human blood, saved a number of postpartum women who had almost bled out. He wrote: "appalled at my own helplessness at combating fatal hemorrhage during delivery" [2].

Blundell experimented by exsanguinating dogs and then reviving them by transfusing arterial blood from other dogs. He concluded that blood replacement had to be species-specific using initially vein-to-vein transfusion (Fig. 1.8). He later introduced the use of the syringe, noting that air must be removed and the problem of clotting: "…the blood is satisfactory only if it allowed to remain in the container for but a few seconds" [24].

Fig. 1.7 Early transfusions were carried out between animals and humans. In this early illustration, blood is transfused from a lamb into a man. Wellcome Library, London (Reprinted under Creative Commons Attribution only license CC BY 4.0)

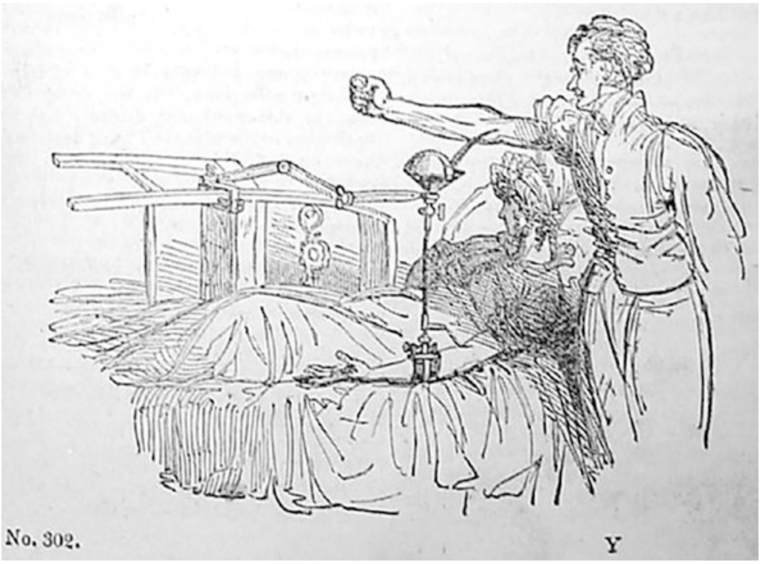

Fig. 1.8 Illustration of Blundell's human-to-human blood transfusion (Source: Blundell J. Observations on transfusion of blood. *Lancet*. Saturday, June 13, 1828; vol. II)

Only with the discovery of the four groups of blood by Karl Landsteiner in 1900 did transfusion become safer and popular again.

(Of note, perhaps, is as recently as 60 years ago, the author of this chapter transfused blood from a young man to a woman during a cesarean section for umbilical prolapse at a small hospital in the mountains of Switzerland. The hospital maintained documentation of the blood type of all the inhabitants of the village. When blood was needed, the type was determined and the appropriate villager instructed to come to the hospital. Basic compatibility was then established and blood drawn in 20 ml aliquots and immediately infused to the patient).

Intravenous Infusions of Drugs and Fluids: Mainly in Dogs

Sir Christopher Wren, along with Robert Boyle, experimented extensively with intravenous administrations of many substances in animals [33]. An animal bladder attached to two quills was designed to infuse beer, wine, opium, and other drugs. A large dog was selected. Venous access was achieved and the vein stabilized with a brass plate. As reported in one of the initial experiments, opium and alcohol were injected (tincture of opium, which had long been used orally) resulting in a brief period of anesthesia. The dog on trying to get up immediately became disoriented. After a period during which the dog was kept moving to assist recovery, a full recovery was made. Thomas Sprat in a history of the Royal Society recorded in 1657: "Wren was the first author of the Noble Anatomical Experiment of Injecting Liquors into the Veins of animals: an experiment now vulgarly known but long since exhibited to the Meetings at Oxford, and thence carried by some Germans and published abroad. By his operation, Creatures were immediately purged, vomited, intoxicated, killed or revived according to the quantity of Liquor injected" [24].

Wren himself described the initial experiments carried out in Boyle's quarters on High Street in Oxford in 1656 in a letter to a friend, William Perry in Ireland: "I have injected Wine and Ale in a living Dog into the Mass of Blood by a Veine, in good quantities till I have made him extremely drunk but soon after he Pisseth it out" [33–36].

It is surprising that given the apparent anesthetic state realized in the dogs that a potential for intravenous anesthesia during surgery in humans was not realized. Difficulty in gaining and maintaining intravenous access, the political climate, wariness regarding the technique, and observations that the amount of drug that would be effective was impossible to judge may all have been factors. It is also possible that the players were more interested in other pursuits—Wren as an architect, Boyle as a chemist, Willis in anatomy of the central nervous system, Robert Hooke as philosopher and machinist [35]. Or these experiments may have been viewed as merely a diversion from the real work of the day.

Early Attempts with Needles and Syringes

Until the beginning of the nineteenth century, infusion of blood and other substances was by direct cannulation of vessels using a quill or some other tube. Basically, a syringe is a simple pump and it is likely that syringe-type devices were produced by many people. The earliest and most common syringe-type device was called a "clyster"—a device for giving enemas. There were numerous parallel processes of evolution and experimentation that led to the development of the hypodermic syringe devices to inject drugs and medicines. Thus, several people have been credited with the "invention" of the syringe. In 1807, the Edinburgh Medical and Surgical Dictionary defined a syringe as: "A well-known instrument, serving to imbibe or suck in a quantity of fluid and afterwards expel the same with violence. A syringe is used for transmitting injections into cavities or canals" [37].

Mr. Fergusson, of Giltspur Street in London, devised a glass syringe, used in 1853 by Alexander Wood for the subcutaneous injection of opiates for the relief of pain [38]. Wood improved on the design, attaching a hollow needle that had been invented by Francis Rynd in Ireland and attaching it to a syringe. He published a description of the subcutaneous injection of fluid drugs for therapeutic purposes in 1855 [39, 40]. Wood believed that the action of opiates administered by subcutaneous injection was mainly localized. Using a syringe, he thought, would allow greater accuracy in administering the drug in close proximity to a nerve, providing better pain relief. Around the same time, Charles Pravaz of Lyon also experimented with subdermal injections in sheep using a silver syringe measuring 3 cm (1.18 in) long and 5 mm (0.2 in) in diameter. Pravas's syringe had a piston that was driven by a screw so he could administer exact dosages. The glass of Wood's syringe allowed for more accurate dosing [36].

Wood also believed that by injecting morphine into the arm, the problem of addiction could be solved [41]. Given orally, morphine increased the appetite but that was not the case if given intravenously [41]. Although it was reported that Wood's wife died of intravenous morphine at his hand, that is probably not true as she outlived him by 10 years, dying in 1894 [41]. During the American Civil War (1861–1865), an estimated 400,000 soldiers became addicted to morphine, a number that may be underestimated as as addiction was not recognized as a medical condition and veterans were at risk of losing their job if it became known that they depended on drugs Given that surgery was traumatic without anesthesia, the use of morphine began to spread. Opium pills were widely dispensed when hypodermic needles were unavailable. During the Civil War, solders were often dosed with enormous amounts of morphine or opium to kill pain. While the potential for addiction was already known, simple humanitarian concerns ensured that soldiers remained liberally dosed with morphine.

Anecdotal accounts of Civil War doctors on both sides dispensing opium are common. One Confederate doctor, William H. Taylor, gave a plug of opium to every patient reporting pain. A Union doctor, Nathan Mayer, diagnosed patients from horseback. If the wounded soldier needed morphine, Mayer would pour out an "exact quantity into his hand and have him lick it off. "Soldiers' Disease" was ascribed to the returning veteran: "…Identified because he had a leather thong around his neck and a leather bag with morphine sulfate tablets, along with a syringe and a needle issued to the soldier on his discharge" [41].

As Kane noted in his book, *The Hypodermic Injection of Morphine*: "There is no proceeding in medicine that has become so rapidly popular; no method of allaying pain so prompt in its action and permanent in its effect; no plan of medication that has been so carelessly used and thoroughly abused; and no therapeutic discovery that has been so great a blessing and so great a curse to mankind than the hypodermic injection of morphia" [42].

The Cholera Epidemic

Clouds have a silver lining could not be more true than what black, thick, cold blood in collapsed and dead patients led physicians to believe that the cure lay in bloodletting, inducing vomiting, and dosing with calomel, this last remedy used as a means of "unlocking the secretions" [43]. By the end of 1832, there were at least 23,000 cases in England with a mortality rate of 33% [43, 44]. The first death in England had occurred in Sunderland on October 26, 1831. There appeared to be a high incidence of cholera in that part of the country, a finding that attracted the attention of a 22-year-old recent medical graduate from the University of Edinburgh, William O'Shaughnessy. He read a paper before the Westminster Medical Society on December 3, 1831, which was later published in the *Lancet*, pointing out the high mortality rate of cholera and asking if: "the habit of practical chemistry which I have occasionally pursued…might lead to the application of chemistry to its cure…(and describing the end result of the disease as)… the universal stagnation of the venous system and the rapid cessation of the arterialization of the blood are the earliest as well as the characteristic effects…hence the skin becomes blue… if…we could bring certain salts of highly oxygenated constitution fairly into contact with the black blood of cholera, we would certainly restore its arterial (oxygenated) properties and most probably terminate the bad symptoms of the case" [45].

Shortly after his address, O'Shaughnessy went to Sunderland to learn more about the disease and the therapies used [46]. He carried out analyses on the blood and excreta of several victims and concluded that the blood "has lost a large proportion of its water…it has lost also a great proportion of its and neutral saline ingredients" [47, 48].

As the disease spread to London, O'Shaughnessy made a further report to the Central Board of Health with "therapeutic conclusions": "the indications of cure…are two in number—viz. first to restore the blood to its natural specific gravity; second to restore its deficient saline matters…the first of these can only be effected by absorption, by imbibition, or by the injection of aqueous fluid into the veins. The same remarks, with sufficiently obvious modifications apply to the second…When absorption is entirely suspended…in those desperate cases…the author recommends the injection into the veins of tepid water holding a solution of the normal salts of the blood" [43].

Although O'Shaughnessy completed detailed analyses of the bodily fluids of many cholera victims, and even experimented with intravenous infusions in animals, he did not extend his treatment to humans, although his descriptions are precise: “When the current of the circulation is impeded, as in the blue cholera, injections from the bend of the elbow can scarcely be efficient. I would, therefore, suggest that the tube, which should be of gold or silver, be introduced into the external jugular vein immediately as it crosses the sternomastoid muscle. The syringes should contain no more than 3 ozs, the solvent should be distilled water heated to a blood warmth and the syringe also equally warmed. The tube should not be more than an inch long and curved gently for the convenience of manipulation and it should have a marked conical form. After the vein is exposed, I would make a puncture with a lancet just sufficient to permit the introduction of the tube. Injection should be deliberately and slowly performed” [49].

While O’Shaughnessy understood the need to replace electrolytes, at about the same time, others had recognized the need for fluid replacement and injected water. Jaehnichen and Hermann, both from the Institute of Artificial Waters in Moscow, during the same cholera epidemic may have injected 6 oz. of water into a cholera patient who appeared to rally briefly but died 2 h later [50, 51]. However, based on a report made later by Jaehnichen, it is doubtful that venous injections were made, rather suggestions were offered [52]. Others also injected water intravenously and a few attempts were made with hypertonic saline but without success [53].

A few weeks after O’Shaughnessy’s publications in the *Lancet*, Thomas Latta, a general practitioner in Leith, adopted the former’s principles. He did not seek publicity or claim originality [44]. He noted that he “attempted to restore the blood to its natural state, by injecting copiously into the larger intestine warm water, holding in its solution the requisite salts and also administered quantities from time to time by the mouth” [44, 49].

Finding that this approach provided no benefit, and indeed sometimes only increased the vomiting and diarrhea, he “at length resolved to throw the fluid immediately into the circulation” [54].

He described his first case, an elderly, moribund woman, who at the start of treatment was pulseless. He inserted a tube into the basilic vein and cautiously began to infuse 6 pints of salt solutions. The patient responded and appeared to have recovered completely. Latta left her with the general surgeon. Unfortunately, a short period later, the vomiting returned and she relapsed and died. Latta wrote: “I have no doubt the case would have issued in complete reaction had the remedy which already had produced such effect been repeated” [54].

Three weeks later, on June 16, 1832, Latta detailed three further cases in a letter to the editor of the *Lancet* [55]. The intravenous infusion consisted of muriate of soda and subcarbonate of soda in 6 pints of water, calculated at 58 meq/l sodium, 49 meq/l chloride, 9 meq/l bicarbonate [44]. The solution was strained through chamois leather. Initially, Latta warmed the solution but later felt it preferable to place the patient in a warm bath. He also increased the saline matter by one third [56, 57]. He recognized that repeated infusions were necessary and in one case he gave 330 oz. over 12 h (about 10 l). The therapy was not immediately accepted, as of the first 25 reported cases, only eight recovered—probably because treatment was delayed until the patients were practically moribund and infusions were not continued after the initial attempts [43]. However, Latta did have one important supporter, Dr. Lewins, a colleague who encouraged him to report his findings to the Central Board of Health. Lewins described the work as "a method of medical treatment which will, I predict, lead to important changes and improvements in the practice of medicine" [58].

In his communication to the Central Board, Latta described how he injected the solution, using Reid's patent syringe. He emphasized the need to avoid accidental introduction of air into the veins [59]. Despite the fact that 12 out of 15 patients treated with intravenous solutions had died, the Board considered this was a favorable result and praised Latta for his scientific zeal [60].

John Mackintosh, a prominent Edinburgh physician was an early supporter of Latta, although he too advocated saline infusion as a last measure [53]. He described the method of infusion that was to be injected at 106–120 °F. Solid particles of saline could be strained through leather rather than linen. Reed's syringe was a large, two-way device with ball valves, connected by a tube that often corroded. Two persons were required for the procedure and up to 5 l could be injected in 30 min [53]. Mackintosh noted that rigors almost invariably followed the infusions, commencing, sometimes, during the infusions. He suggested that the fluid should be made as close as possible to serum and added albumen from eggs to the solution, without apparent improvement. Mackintosh felt that as the survival from cholera was only 1:20 in severe cases and 1:6 with saline infusions, the latter therapy was beneficial [53]. Sugar, cod liver oil, milk, and honey were all suggested as additives, but few other advances were made [61].

Improving the Infused Solution

The cholera epidemic died down in Britain and physicians became less intent on replacing fluids intravenously. The main protagonists of the practice were no longer around. Latta died in 1833 and O'Shaughnessy went to India where he became involved in developing telegraphic communications and also later introduced the therapeutic use of *Cannabis sativa* to Western medicine for the treatment of tetanus, epilepsy, and rheumatism [62].

But cholera continued in the Americas. Nevertheless, the use of intravenous saline was not generally accepted. It was often given only to those who were about to die and the public felt that the therapy hastened death. Also, not understanding that severely dehydrated patients can no longer lose fluids, it was felt that rehydration would provoke further purging. Treatment was rarely continued as Latta had suggested. Perhaps also and of equal importance, the fluid was not sterile, chemically impure, and very hypotonic. Thus, the more fluid that was infused, the greater the risk of bacteremia, fever, and hemolysis [43]. Many patients who might have recovered from cholera either died quickly of air embolism or slowly from sepsis [50].

Gradually, over the next 100 years principles of asepsis and anesthesia developed. The notion that disease could be transferred by very small particles was raised by an Italian physician, Girolamo Fracastoro, in the sixteenth century. He authored a book in which he expounded on his theories, but they were not widely accepted [63]. He used the Latin word *fomes* in 1546, which means tinder, implying that books, clothing, etc., can harbor and hence spread disease. From this word comes "fomites."

Some 200 years later, and shortly before Louis Pasteur's work, Agostino Bassi, an Italian entomologist, introduced the idea of microorganism as a source of disease [64]. Pasteur, working in Paris in the second half of the nineteenth century, developed the concept that without contamination, microorganisms cannot grow [65, 66]. Using sterilized and sealed flasks he demonstrated that nothing developed until the flasks were opened. Joseph Lister, professor of surgery at the University of Glasgow, furthered the idea of antisepsis and the germ theory of disease, noting especially the importance of clean wounds in surgery to allow healing [67]. At that time, a mark of a good surgeon was the amount of dried blood he had on his coat, often a black frock coat. Lister used carbolic sprays in his operating theaters at the Glasgow Royal Infirmary (Fig. 1.9). He also noted that the infection rate in the wards of the hospital that abutted the necropolis was greater than at the other end—perhaps due to the decomposing bodies that awaited burial outside the windows on the cemetery side. Over three papers to the *British Medical Journal* and the *Lancet*, he laid out the necessity for germ control [67–69].

Concurrently, other advances in the understanding of intravenous solutions were made. Jean-Antoine Nollet first documented observation of osmosis in 1748 [70] and Jacobus Henricus van't Hoff, a Dutch physical chemist, was awarded the Nobel Prize for Chemistry in 1901, for work on rates of chemical reaction, chemical equilibrium, and osmotic pressure [71].

Attention again returned to infused solutions. A few studies were carried out in 1882–1883 by a Dutch physiologist, Hartog Jacob Hamburger, on concentrations of salt solutions. He deduced, based on looking at red cell lysis, that 0.9% was the concentration of salt in human blood. In 1896, he described the crystalloid solution known as Hamburger's solution or normal saline. Based on plant-based experiments by a botanist, Hugo de Vries, Hamburger developed a salt solution that was thought

Fig. 1.9 Lord Joseph Lister's carbolic spray in the Hunterian Museum at the University of Glasgow

to have the same osmolality as human blood and therefore could not hemolyze red blood cells. Whether saline was ever originally intended for intravenous administration is not known [72]. Matas in the United States published a case report of the use of an IV infusion of saline for the treatment of shock in humans [73]. Some years later, he described a continuous “drip” technique using glucose [74].

The next major advance came from a British cardiovascular physiologist, Sidney Ringer, who was attempting to study isolated hearts, also during the 1880s, to determine what might keep them beating normally [75]. He used a saline solution consisting primarily of sodium, potassium, and chloride ions, with an added buffer using distilled water to prepare his solutions. However, he found that the isolated heart muscle soon failed to contract. A somewhat anecdotal story reports that one day cardiac action continued for hours [76, 77]. Apparently, having run out of distilled water, a lab technician had used river water, which contains many minerals including calcium. This accidental discovery led to the finding that heart muscle, unlike skeletal muscle, requires extracellular calcium to contract.

During the 1930s, Ringer’s solution was further modified by an American pediatrician, Alexis Hartmann, for the purpose of treating acidosis. He added lactate to attenuate changes in the pH by acting as a buffer for acid. Thus, the solution became known as “Ringers lactate solution” or “Hartmann’s solution” [78].

Another important development came with the realization that despite sterilization, febrile reactions were still common. Seibert discovered in 1923 that sterilized and stored metabolic by-products of microorganisms, pyrogens, were formed if distilled water was not used [79].

Needles and Syringes

Now that sterilization and osmolarity were better understood, means to infuse fluids more conveniently and safely became important.

As noted earlier, Wood can be largely credited with the popularization and acceptance of injection as a medical technique, as well as the widespread use and acceptance of the hypodermic needle [39, 40]. But the basic technology of the hypodermic needle stayed largely unchanged as medical and chemical knowledge improved. Small refinements were made to increase safety and efficacy, with needles designed and tailored for particular uses after the discovery of insulin. Banting, a Canadian surgeon had persuaded John Macleod in Toronto to lend him some lab space. During the latter’s absence and working with his assistant Charles Best, they were able to identify insulin (named after the Islets of Langerhans) in 1921 [80]. Insulin was to be given intravenously.

During the early part of the twentieth century, “IV feedings” were only given to the most critically ill patients. Fluids, usually boiled, were poured into an open flask, which was covered with gauze. A rubber stopper attached to either glass or rubber tubing was inserted into the neck. An extra needle was pushed through the stopper for venting purposes. The bottles were all reused as was the tubing. A metal screw clamp allowed for flow adjustment. A nurse stayed with the patient during the infusion [81]. Hospital pharmacies usually made their own solutions. Cleansing the skin with alcohol prior to needle insertion was not common practice. Needles were large, usually 14–16 g, and also reusable (Fig. 1.10a–e). Most were made of steel. A stylet kept the lumen open. Small, 1-in., 22 gauge scalp vein needles for babies were also available. There were three main methods of intravenous administration of drugs: a new venipuncture each time, a continuous infusion through a hypodermic needle, and venous cut-down. This last technique, usually performed at the ankle, required tying off of the vein, prior to its opening and threading in a small plastic catheter. Prior to the advent of autoclaving in the 1950s, all materials were sterilized with boiling water. Even gauzes, usually handmade, were sterilized in metal canisters and accessed using sterile forceps.

Fig. 1.10 (**a**–**e**) An assortment of early needles and syringes

Anesthesia was also advancing from the early days of inhalation agents. In 1869, Oskar Liebreich advocated chloral hydrate as an induction agent [82], a technique put into practice briefly by Pierre-Cyprien Ore in 1872 [83]. However, the high mortality rate discouraged use of this drug. David Bardet used "Somnifen" in 1921 [84]. This barbiturate derivative had a low solubility and long duration of action but was also not well received. However, the idea of an induction agent was considered of considerable value to allay the fears of patients before entering the operating room. "Pernosten" was introduced in 1927, and in 1932 [85], Weese and Scharpff synthesized hexobarbital [86].

Volwiler and Tabern, working for Abbott Laboratories, discovered pentothal in the early 1930s [87]. Ralph Waters in Wisconsin first used it in humans in March 1934. He found the drug to have short-lived effects and little analgesia. Some 3 months later, John Lundy at the Mayo Clinic started a clinical trial of thiopental [88]. Although reported at the time, thiopenthal probably was not responsible for large numbers of deaths at Pearl Harbor. A more recent report suggests gross exaggeration: Out of 344 wounded that were admitted to the Tripler Army Hospital only 13 did not survive, and it is not likely that thiopental overdose was responsible for more than a few of these [89].

Although induction doses of IV anesthetics became the norm, fluid infusions were not necessarily added. Certainly through the 1960s in Great Britain, it was standard practice to secure a vein with a right-angle steel needle. A moveable arm with a rubber patch on the outside of the skin was then moved to cover the hole of the needle within the vein. Should fluid or blood be required, small amounts could be injected via syringe or by presterilized and packaged infusion set. These sets did not have filters when blood was given (personal recollection, Glasgow Royal Infirmary 1963).

During World War II, partially disposable syringes were developed for administration of morphine and penicillin in the battlefield. Working independently during the 1940s, Meyers and Zimmerman devised through the needle cannulation with a flexible tube to allow indwelling catheters that afforded greater mobility to patients over rigid needles [90, 91]. Thrombosis within the catheter was decreased by the addition of silicone. Massa, Luny, Faulconer, and Ridley introduced an apparatus in 1950 consisting of a metal needle stylet, a cannula hub, and an indwelling plastic cannula that was the forerunner of the catheter around the needle design [92, 93]. It became known as the Rochester needle, to be sold in unsterile packages of 12 (Fig. 1.11) [94]. Lundy later refined the design to a two-piece plastic catheter over a plastic stylet in 1958 [95]. The same year, an anesthesiologist from Colorado, George Doherty, came up with the scheme for the intracath: a plastic catheter through a steel needle [96].

Plastics were also becoming more commonly used [97, 98]. Baxter Travenol, a major manufacturer of intravenous equipment, was founded in 1931. The first IV solutions were marketed by that company in vacuum bottles by 1933 [61]. But the complications of IV infusions remained high, such that one physician predicted that "this is a passing new-fangled notion" [61].