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Intravenous Infusions: Past and Present

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Abstract

Intravenous (IV) therapy has undergone significant evolution, transitioning from early experimental approaches to a fundamental component of modern medical practice. The concept of delivering fluids directly into the bloodstream dates back to antiquity, with historical references in religious texts and early medical experiments by alchemists and physicians. However, the formal development of IV therapy began in the 17th century, enabled by scientific advancements that allowed direct bloodstream access. One of the first successful recorded IV infusions occurred in 1665, when English physician Richard Lower performed blood transfusions in animals. Subsequent human blood transfusion experiments were conducted by Christopher Wren and later Robert Boyle.

Advancements occurred during the 19th-century cholera epidemic. IV therapy remained rudimentary until the 20th century, when further advancements standardized and popularized its use.

Keywords: Intravenous therapy, therapeutic advancements, medical history, cholera, patient care

The Early Years of IV Therapy

As Leviticus 17:11 and Genesis 9:4 noted, "The life of the body is the blood." This depiction in the Bible illustrates that the flow of fluids through the body is indispensable for sustaining life. (1, 2) References to IV therapy appear in the classical literature, including the story of the Argonauts. (3) The Roman poet Ovid recounts how Princess Medea rejuvenated her father-in-law by draining his blood and refilling his veins with a restorative potion. (3)

Ancient Chinese medical texts describe how blood is controlled by the heart and flows continuously throughout the body without end, emphasizing the importance of uninterrupted circulation for maintaining health. (4)

Galen believed that blood was produced in the liver and moved back and forth until it was consumed by the body. (5, 6) Although incorrect, this theory dominated medical thinking for many centuries. (7) It was not until 1492 that Girolamo Savonarola attempted to revive Pope Innocent VIII by administering blood from three young donors. (8) Although unsuccessful, this marked the beginning of human experimentation with blood transfusion.

In the 13th century, Ibn al-Nafis made significant contributions by describing pulmonary and coronary circulation. (9) This was followed in 1628 by

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William Harvey, who published his theory on the circulatory system, explaining blood dynamics in a manner similar to our modern understanding and challenging prevailing beliefs. (10) Inspired by Harvey's work, Richard Lower identified physiological causes for differences in blood. (10) Around the same time, Francisco Colle, presumably aware of Harvey's findings, believed that blood could be used to prolong life. (11)

In 1656, Christopher Wren attempted IV drug administration in dogs. He developed a rudimentary version of an IV system using an animal bladder attached to two quills. (12) By 1662, Johann Daniel Major had performed the first IV infusion by injecting a medicinal substance into human circulation (see Figure 1). (13) In 1665, Richard Lower performed the first animal-to-animal blood transfusion by exsanguinating a medium-sized dog and introducing blood from a larger dog until the first showed signs of overfilling. (10, 14, 15) Both animals survived the procedure, providing proof of concept for blood transfusion (see Figure 2).

Two years later, in 1667, Jean-Baptiste Denis performed the first animal-to-human transfusion following Lower's experiments (see Figure 3). (16) He transfused 9 ounces of lamb's blood into a young man, repeating the procedure twice. The initial transfusion was tolerated, but after the second one, the patient suffered one of the earliest documented transfusion-induced reactions. (16)

Despite these advancements, IV therapy faced significant challenges. In 1668, the French Parliament banned animal-to-human transfusions due to concerns about safety and ethics. (17) Six months later, Richard Lower attempted the procedure in England, where no government restrictions were in place. (18) Like Denis, he transfused sheep's blood into a young man with no adverse reactions documented. (18) In 1667, with Lower's assistance, Edmund King successfully administered 12 ounces of sheep's blood to a man. (19) This experiment and others led Lower to develop improved devices to ensure successful transfusions. However, growing concerns over potential adverse reactions led the British Royal Society to ban blood transfusions in 1668; this prohibition was later reinforced by the Vatican in 1669. (20)

The Role of Cholera in the Development of IV Infusions

A pivotal moment in the development of IV infusions occurred in 1817 when cholera first began spreading in India. (21) By 1830, cholera had begun its dissemination throughout the world. (22) A year later, cholera arrived in England. (21)

Sir William O'Shaughnessy Brooke was sent to India to analyze the excretions and blood of cholera patients to determine how they differed from healthy specimens. (23) In his analysis, he identified and reported the differences between normal and cholera-infected blood (see Figure 4). His findings revealed that cholera patients had a 30% water deficiency compared with normal blood. (23) Moreover, he identified the sequence in which blood equilibrium must be restored when administering therapy: "One must reestablish the gravity of blood before the salt-like and carbonate deficiencies of the sample itself." (23) Based on these findings, he considered the possibility of injecting warm water along with the deficient salt and carbonate molecules into a patient. (24) His method of choice was to insert a small gold or ivory tube into the external jugular vein. (25) Edward Stevens, a physician from the West Indies, observed that patients with yellow fever tended to have darker blood and administered oral salt solutions to restore its red color, not for hydration. (24)

Inspired by O'Shaughnessy's findings, Thomas Aitchison Latta developed a liquid solution for treating cholera patients. (22) Latta's solution contained sodium chloride, distilled water, and sodium bicarbonate. (26) His first experiment involved a cholera patient who had not improved with existing treatments. After receiving 6 pints of this solution, the patient initially felt relief, saying she was "freed from all uneasiness." (27) However, the improvement was brief, and she expired a few hours later. (23)

At the time, IV therapy was highly controversial due to the high incidence of complications, such as phlebitis. (28) Many factors contributed to these failures, including infrequent treatment, chemically impure salts, and hypotonic solutions that were insufficient for fluid replacement. Additionally, the use of unsterile fluids frequently led to infections. (28)

This surge of research was short-lived, as interest waned following the end of the cholera pandemic. With Latta's death, the popularity of IV therapy declined. By 1837, James Macintosh attempted to replicate the consistency and composition of human plasma by introducing albumin from eggs. (29) In 1847, Edmund A. Parkes described a case in which he administered 4.5 pints of saline solution along with the albumin of an egg to a cholera patient. (30) Initially, he described the procedure as a success, but the patient later developed "vigorous rigor" and died. (30)

During the second cholera pandemic, milk became the primary component of IV infusions. (29, 31) James Bovell was the first to attempt this approach, injecting 12 ounces of cow's milk, but was unsuccessful. (29, 31) Later, William Howe in New York and James Meldon in England experimented with goat and human milk infusions. (29) However, this practice was quickly abandoned as reports demonstrated that saline solutions were more efficacious than milk infusions. (32)

The Basis of Development and the Evolution of IV Therapy

The development of new materials for IV therapy was only possible with a foundational understanding of human physiology and the need for such treatments. In 1850, Carl Schmidt described the pathophysiology of dehydration. (32) Building on this foundation, Claude Bernard elucidated the concept of extracellular fluid in 1859, contributing to understanding fluid balance within the body. (33) By 1887, Jacobus Henricus van 't Hoff introduced the concept of osmosis, further expanding the understanding of fluid movement across cell membranes. (34) The discovery of electrolyte ionization in 1903 added another layer of understanding essential for maintaining homeostasis in the body. (25) Between 1906 and 1920, Lawrence J. Henderson provided a detailed description of hydrogen ion equilibrium, which was crucial for understanding acid-base balance. (35) These developments collectively laid the groundwork for recognizing the potential and efficacy of IV fluids.

In 1855, Alexander Wood of Edinburgh created the first hypodermic needle-syringe, improving the mechanics of IV infusions and reducing patient trauma. (36) In 1856, Benjamin Barker introduced this needle to the United States at Bellevue Hospital. By the early to mid-20th century, a major advancement was the development of interchangeable parts, allowing glass syringes to be sterilized and reused up to 20 times before replacement. However, additional challenges remained, such as the need for precise resharpening of needles to maintain effectiveness and safety. (37)

In 1882, C. Egerton Jennings reported using a solution containing 20 ounces of warm water (100ºF), 50 grains of sodium chloride, 3 grains of potassium chloride, 25 grains of sodium sulfate, 25 grains of sodium bicarbonate, 2 grains of sodium phosphate, and 2 drachms of absolute alcohol for the resuscitation of a woman with severe obstetric hemorrhage. (38)

By 1892, Charles Spencer first used the term "normal salt solution" but failed to describe the components of the fluid. (39) In 1896, Hartog Jacob Hamburger created a physiological serum to aid in his research on the hemolysis of red blood cells. (40) He did this by comparing the freezing points of NaCl solutions with the blood of mammals and amphibians. He concluded that mammalian blood and 0.9% NaCl had a similar freezing point, while amphibian blood had a freezing point comparable to that of a 6% NaCl solution. (40, 41) This led him to determine that his solution was compatible with blood and did not cause hemolysis. In 1906, Frances Alexis Carrel created a sodium chloride solution similar to plasma, which he used to maintain tissue outside the human body. (32)

The use of 0.9% NaCl solution in infusion therapy became widespread following canine experiments. (40) In 1886, British physiologist Sidney Ringer experimented on frog hearts using distilled water and observed changes in their contractility as the heart absorbed the fluid. (42) His goal was to create a solution that could support the heart's contractility for an extended period while immersed in it.

Ringer observed that potassium salts affected ventricular dilation in a manner similar to blood. Weeks later, he discovered that the saline solution he had used for his experiments was prepared with tap water rather than distilled water. (42) This realization led him to recognize the crucial role of electrolytes and extracellular fluid in heart function. He noted the presence of potassium, calcium, and chloride (see Figure 5). Based on this finding, he developed a refined version of the tap water solution, optimizing its electrolyte composition. This new formulation became known as "Ringer's solution." (42, 43)

With the solutions available at the time, aggressive resuscitation was ultimately implemented by Walter Cannon in 1918. However, he proceeded cautiously, advising that surgeons should first control the primary bleeding before initiating IV infusions to prevent potential complications. (43)

During World War I (WWI), it became evident that a standard saline solution was insufficient for providing adequate hemodynamic stability. Bruce Robertson was the first to use blood transfusions during WWI, successfully transfusing 22 wounded soldiers. By 1925, blood transfusions were also used to treat burns. (15)

In 1932, Alexis Hartmann modified the original Ringer's solution by adding lactate to improve its effectiveness in children. (44) He observed that chil-

dren were dying from hyperchloremic acidosis due to significant sodium loss. His modification reduced the incidence of acidosis and minimized the adverse effects of standard Ringer's solution. (44)

One of the earliest IV colloids was organic gum Arabic, derived from the *Acacia senegal* tree. This mixture of polysaccharides and glycoproteins was widely used during WWI but was discontinued in 1937 due to adverse effects and contraindications. (45)

In 1939, German chemistry professor Walter Reppe developed a 4% colloid solution, later known as Periston. (46) By the 1950s, advancements in IV administration technology enabled the use of gelatin as a colloidal solution. In the 1960s, Periston was discontinued because its molecules were not easily degradable and accumulated in body tissues. (46) During this period, starch-based and other colloidal solutions became standard, as they were generally more effective than crystalloids. (47)

Another notable wartime product innovation emerged during the Vietnam War in 1955: the use of coconut water as an IV infusion for soldiers. (46, 47) Coconuts were readily available, and their water was sterile when extracted from an unopened coconut. Its molecular composition resembled intracellular plasma, with low sodium and high potassium content. (47) No adverse effects were recorded; to this day, coconut water remains an emergency IV measure in some countries. (47)

Stanley Dudrick's administration of protein hydrolysates and dextrose as IV nutrition marked a key innovation, successfully nourishing six puppies and later sustaining a newborn for 15 months, laying the foundation for total parenteral nutrition, which was FDA-approved in the 1970s. (48)

Intravenous Access

Initially, IV therapy relied on peripheral catheters, which limited nutrient delivery due to the risk of hyperosmolarity. From Wood's early development through 1950, IV sets consisted of reusable steel needles with a stylet inside. David Massa later modified the needle length, inserting a second steel needle as an inner stylet, which was then covered with a polyvinyl chloride catheter. (49) This innovation became known as the Rochester Needle. However, these needles were packaged with others that required sterilization before each use. (49)

In 1953, Sven Ivan Seldinger developed the "Seldinger technique" for vascular access. This technique involved a guidewire, an integrated needle, and a catheter, significantly reducing patient trauma and eliminating the need for surgical placement. (50, 51, 52)

In 1956, Colin Murdock developed the plastic disposable syringe. In 1958, George Doherty introduced the modern catheter—a plastic device inserted through a steel needle and individually sterilized and packaged. This advancement, along with Carl Walter's introduction of aseptic techniques and the widespread adoption of the autoclave in 1958, significantly increased the use of IV fluids. (49)

A pivotal advancement in IV therapy came with Dr. Holliday and Dr. Segar's landmark 1957 paper, which introduced a formula for calculating fluid requirements based on a patient's age, weight, insensible water loss, and renal losses. This formula was so significant that it remains widely used today as a fundamental component of medical care. (53) Despite the long-standing use of IV therapy, no formal regulations were implemented until 1992, when the National Institute for Health and Care Excellence (NICE) issued guidelines to ensure safe and effective fluid administration.

Conclusions

The development of IV therapy traces its evolution from rudimentary experiments to an essential component of modern healthcare. Early innovations, such as Richard Lower's blood transfusions and Thomas Latta's saline infusions, were pivotal in advancing fluid replacement therapy, driven by the urgent need to treat life-threatening dehydration and blood loss. Over time, a deeper understanding of fluid balance, along with advancements such as sterile equipment and disposable syringes, contributed to the widespread adoption and standardization of IV therapy.

Today, IV therapy is indispensable across medicine, with regulatory protocols and clinical guidelines ensuring safety and efficacy while reflecting lessons from past challenges and innovations. The history of IV therapy highlights the profound impact of medical ingenuity on patient care, with each milestone paving the way for new advancements. As medical science evolves, IV therapy's legacy underscores the need for continuous refinement to meet complex patient needs, reinforcing the vital role of research and innovation in shaping the future of healthcare.

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Figure 1. Johann Daniel Major describes his method for performing intravenous infusions in his book *Chirurgia infusoria, placidis cl. virorum dubiis impugnata, cum modesta, ad eadem, responsione*. (Kiloni [Kiel]: Sumptibus Joh. Lüderwald; imprimeb. Joach. Reumannus, 1667:2).

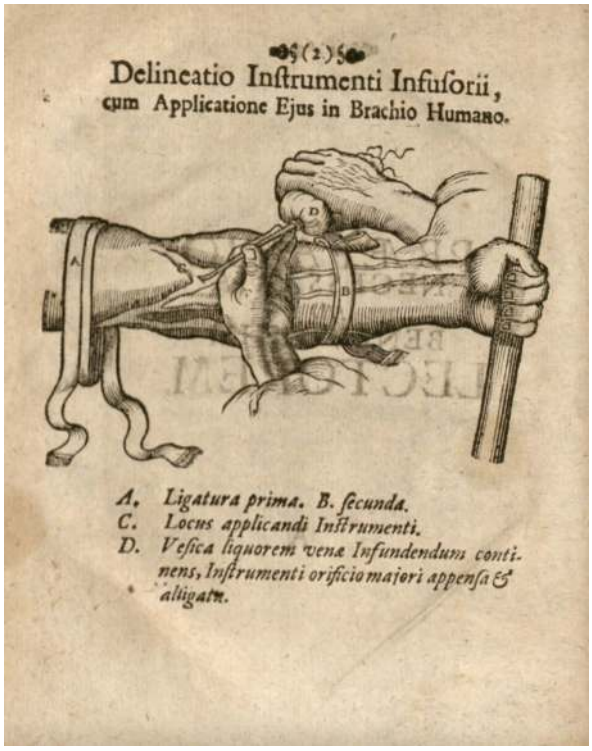


Figure 2. Engraving depicting transfusion in the neck and leg of a dog, from animal to human, and from human to human, by J. S. Elsholtz, 1667. Wellcome Library, London. CC BY.

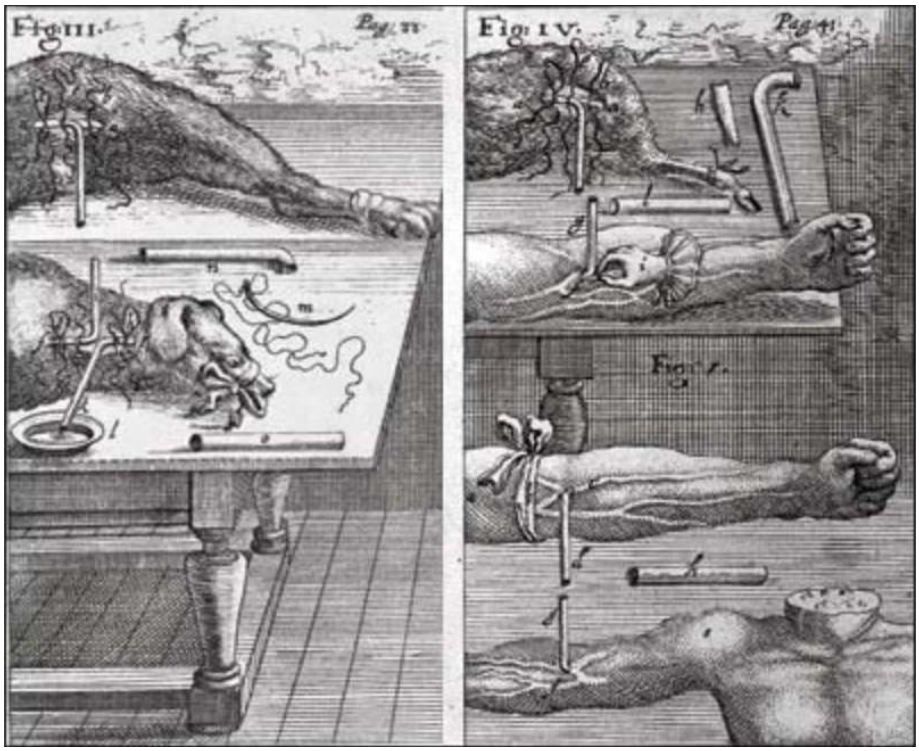
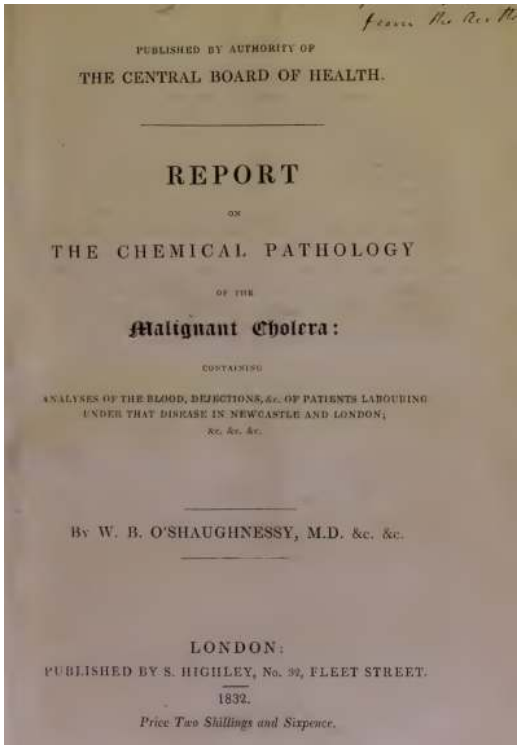


Figure 3. Portrayal of blood transfusion from animal to human by Dr. Jean Baptiste Denis. From Matthias Gottfried Purmann's *Grosser und gantz neugewundener Lorbeer-Krantz, oder Wund Artzney…Zum andern Mahl vermehrt herausgegeben* (1705).



Figure 4. *Report on the Chemical Pathology of the Malignant Cholera,* by W.B. O'Shaughnessy. London: S. Highley.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REPORT
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ANALYSES OF THE BLOOD, DEJECTIONS, &c. OF PATIENTS LABOURING UNDER THAT DISEASE IN NEWCASTLE AND LONDON;
&c. &c. &c.

By W. B. O'SHAUGHNESSY, M.D. &c. &c.

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Figure 5. *A Further Contribution Regarding the Influence of the Different Constituents of the Blood on the Contraction of the Heart,* by Sydney Ringer.

A FURTHER CONTRIBUTION REGARDING THE INFLUENCE OF THE DIFFERENT CONSTITUENTS OF THE BLOOD ON THE CONTRACTION OF THE HEART.

By SYDNEY RINGER, M.D., *Professor of Medicine at University College, London.* (Plate I.)

After the publication of a paper in the Journal of Physiology, Vol. III., No. 5, entitled "Concerning the influence exerted by each of the Constituents of the Blood on the Contraction of the Ventricle," I discovered, that the saline solution which I had used had not been prepared with distilled water, but with pipe water supplied by the New River Water Company. As this water contains minute traces of various inorganic substances, I at once tested the action of saline solution made with distilled water and I found that I did not get the effects described in the paper referred to. It is obvious therefore that the effects I had obtained are due to some of the inorganic constituents of the pipe water.

Water supplied by the New River Water Company contains 278·6 parts of solids per million.

They consist of:

Calcium	38·3	per million.
Magnesium	4·5	„
Sodium	23·3	„
Potassium	7·1	„
Combined Carbonic Acid	78·2	„
Sulphuric Acid	55·8	„
Chlorine	15	„
Silicates	7·1	„
Free Carbonic Acid	54·2	„

This water is faintly alkaline to test-paper from bicarbonate of lime. Saline made with this water I found at first rounds the top of the trace of each contraction and later greatly prolongs diastolic dilatation, and that these effects are completely obviated by about 1 c. c. of 1 % solution

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