Preface

Perfusionists are primarily known for supporting patients in the cardiac operating room, while on cardiopulmonary bypass. Over the last decade, perfusionists have expanded their expertise to include extracorporeal membrane oxygenation program development and management, ventricular assist device management, intra-aortic balloon counter pulsation, hemofiltration or dialysis during or post cardiac surgery, pacemaker programming, anticoagulation management of HIT-patients, isolated organ perfusion for chemotherapy, and blood gas management. Furthermore, there are additional responsibilities in catheterization laboratories, as well as in research studies and publications. While the roles and responsibilities of a perfusionist can vary from hospital to hospital, the complexity and variety of tasks performed require extensive training and education, both in theory and practice.

After the first successful German edition of "Extracorporeal Circulation in Theory and Practice" in 1999, Rudi Tschaut started a new project in the Spanish language. Together with co-editors Eligio Garcia and Juan Leon-Wyss, the first Spanish textbook for perfusionists was published in 2003. The German book was sold out after two years so it was decided to edit an updated second edition, which was published in 2005.

Since that time, Rudi changed his clinical environment and transitioned to the medical device industry, with a strong focus in extracorporeal technologies. In the summer of 2017, many years after the first edition, he met the publisher Wolfgang Pabst by coincidence at a congress in Leipzig. Because of Rudi's relationship with the US market, Wolfgang asked him to initiate a new "transatlantic" book project for perfusionists. He thought the book should be written in English and include both European and American authors. After a couple of days, Rudi called back and told Wolfgang that he would like to organize such an outstanding project if he could find a couple of willing co-editors in the US. Therefore, at the end of 2017, Rudi reached out to Tami Rosenthal at Children's Hospital of Philadelphia and Ashley Hodge at Nationwide Children's Hospital, whom he had met in the past, and explained the idea of such a challenging book project. Both of them immediately agreed to be part of the team, not knowing the tremendous workload that must be accomplished. The next step was to plan the content of the new book around current topics. At the beginning of 2018, we reached out to authors from the first edition across Europe as well as to new authors in the US, and invited them to be part of this project. Because of the intensive review process, and the large amount of international multidisciplinary authors, additional help was needed and we asked Molly Dreher from Children's Hospital of Philadelphia if she would like to be part of the team and thankfully she agreed.

After 2 ½ years of extensive efforts, we are very proud to serve as editors of a very special, international textbook in English. We thank all our clinical colleagues and scientists in perfusion, cardiology, anesthesia, cardiac and pediatric cardiac surgery, physiology, pharmacy, and pulmonology around the world who contributed to this unique book. We also would like to thank the team from the Pabst Publishing House who contributed their ideas, energy and time to this project: Wolfgang Pabst, who supported us during the whole period, Erika Wiedenmann, who translated all German articles into English and managed the project, Visnja Kabalin Borenic, who performed the language editing and Armin Vahrenhorst & Patrick Orths, who designed the book cover and typeset all of the chapters. Finally, we thank our families for their patience and support.

This book is intended to serve as a comprehensive review for perfusionists, surgeons, anesthesiologists, pulmonologists, pediatricians, neonatologists, ICU nurses and ECMO specialists and we believe that it will help to enhance theoretical and practical knowledge and understanding for extracorporeal treatments.

Rudolf Tschaut
Tami Rosenthal
Ashley Hodge
Molly Dreher

Introduction to Extracorporeal Circulation in Theory and Practice

Among the greatest advances in healthcare that have led to an unprecedented increase in life expectancy in the 20th century is the development and mass production of the extracorporeal circulation machine. This complex device is capable of supporting end organ function for extended periods of time, permitting the surgeon to repair previously lethal heart and vascular defects. This accomplishment was a culmination of a series of events that enabled the development of the technology, as well as its manufacturing at a scale and cost that would permit application worldwide. While it is tempting to ascribe any one event as seminal in its development, such as Ludwig Rehn's successful suture of a right ventricular stab wound, McLean and Howell's discovery of heparin in 1916, and the use of protamine to neutralize heparin in vivo in 1939, it is John H. Gibbon in 1953 who is credited with the first successful use of this technology to repair a heart defect under direct visualization. As with many advances in the field of cardiac surgery, the initial efforts were fraught with difficulties and complications, which in Gibbon's case resulted in his abandonment of the technology. Fortunately, others, such as Richard de Wall, who refined the bubble oxygenator, and John Kirklin, who simplified the pump and circuit, took up the efforts and overcame the many hurdles they faced.

Since the early days of the roller pump and bubble oxygenator, a steady stream of technologic innovations has resulted in advances not only in extracorporeal circulation technologies and methods, but also in adjunct technologies such as medical devices and implants, including heart valves, blood vessel substitutes, and pacemakers, to name just a few. In parallel, research work to understand the effect of extracorporeal circulation on the body's end-organs, coagulation, and immune system has led to further refinements in the components of the circuit as well as the techniques for managing perfusion. Currently the science and practice of extracorporeal circulation spans the medical fields of anatomy, physiology, endocrinology, immunology and coagulation, as well as the function of individual organs including heart, lungs, brain, kidneys, liver, and pancreas. Extracorporeal circulation also spans the engineering fields of fluid mechanics, materials science, electronics, and an increasing role for computer science and data analysis. Indeed, to completely cover all aspects of extracorporeal circulation, particularly the many applications in a wide variety of therapies, would require a multivolume text.

The current edition of Extracorporeal Circulation in Theory and Practice, edited by Tschaut, Rosenthal, Hodge, and Dreher, offers a masterful balance of the basic science and theory behind current technology and current methods of perfusion, its benefits and complications. The text begins with a review of the advances in extracorporeal circulation, followed by an introduction to the relevant anatomy and physiology of the cardiovascular system, and hematologic response to external perfusion.

A review of the more common surgical procedures on the heart and great vessels is followed by an introduction to trans-catheter techniques that are rapidly becoming an integral part of cardiovascular therapy.

The next four sections cover fundamental principles in the science of extracorporeal circulation as well as core engineering concepts that explain how mechanical perfusion is achieved and gas exchange controlled in current circuits. Practical aspects of perfusion are also covered such as cannulation techniques and devices and management of the circuit, along with myocardial protection methods.

The subsequent sections address specific aspects of extracorporeal circulation such as mechanical circulatory assistance, complications of bypass, special techniques for organ perfusion and methods for long-term support. The final sections cover the frontiers of the cardiovascular field.

To cover these diverse topics, the editors have gathered an impressive and long list of experts in the specific fields, representing institutions from Europe and North America. This text offers a comprehensive and up to date source of information for the student as well as the experienced professional in the fields of perfusion, cardiovascular surgery, transplantation, anesthesia, intensive care, and cardiac nursing.

Pedro J. del Nido, M.D.

1

History of Perfusion

The History of Extracorporeal Circulation

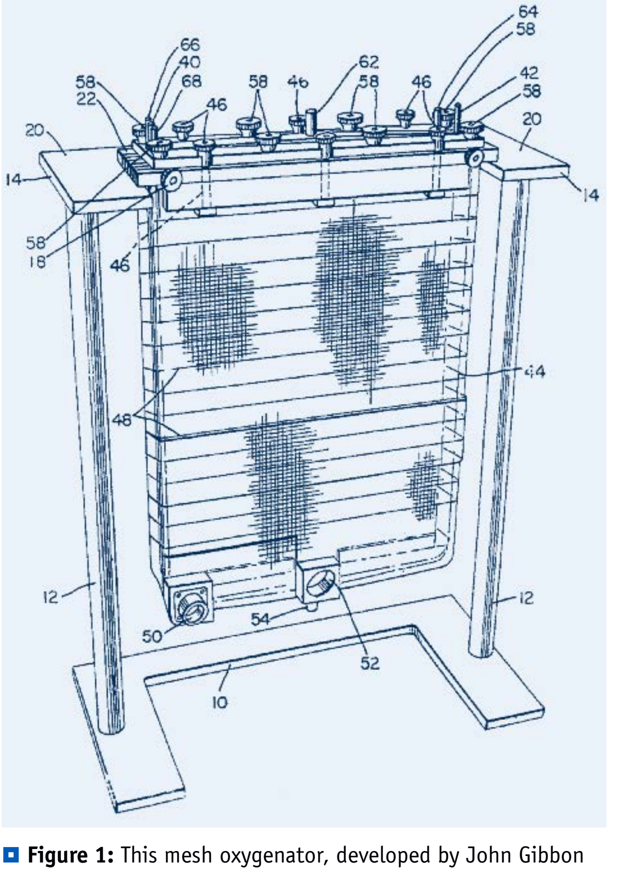
Wolfgang Böttcher

Nearly 70 years ago, open heart surgery was performed for the first time with the help of extracorporeal circulation. Research efforts of several working groups on heart-lung machines progressed to the point of clinical application. In Turino (Italy), on August 9, 1951, a 49 year-old patient of Achille Mario Dogliotti and A. Constantini survived partial bypass with a perfusion flow of approximately 1 l/min. Dogliotti's heart-lung machine, which was already prepared prior to the surgery, consisted of roller pumps and an oxygenator functioning according to the gas dispersion principle. During the dissection of a large mediastinal tumor, the patient collapsed due to compression of the venae cavae and of the right heart [1]. From the beginning of 20 minutes of extracorporeal circulation, blood pressure and sufficient gas exchange were restored. With this temporary circulatory support, it was possible to resect a large part of the tumor. After this first successful clinical use of a heart-lung machine in a human, Dogliotti wrote: "We are convinced also that it can be usefullyadopted during major surgical operations, especially on the heart and brain, and also can be associated with controlled hypothermia" [2].

A few months earlier, on April 5, 1951, Clarence Dennis (Minneapolis) for the first time performed open heart surgery with total cardiopulmonary bypass in a 6 year-old female patient [3] . However, neither this patient, nor a second patient who underwent an operation only a few weeks later, survived the operation. Despite the deaths of these two patients, Dennis stated that a functional heart-lung machine had been developed that would have a place in the further development of heart surgery. Dennis had combined a rotating mesh screens oxygenator with membrane pumps according to Dale-Schuster.

In the following year, Forest Dewey Dodrill (Detroit) performed a successful operation using special blood pumps. The setup, however, did not involve an artificial extracorporeal oxygenation system. The blood pumps had been developed in collaboration with the automotive manufacturer General Motors. With the help of a left-heart bypass, Dodrill successfully performed mitral valve surgery on July 3, 1952. Some months later, on October 21, 1952, he used right-heart bypass to perform a successful pulmonary valve operation in another patient [5] .

Finally, it was John Heysham Gibbon jr., who, after decades of preliminary work starting in the 1930s, was able to successfully perform a total cardiopulmonary bypass surgery [6]. On May 6, 1953, Gibbon closed an atrial septal defect in an 18 year-old female patient [7]. Total cardiopulmonary bypass (CPB) was maintained for 26 minutes with the heart-lung machine (Model II) which he had constructed in cooperation with the International Business Machines Corporation (IBM). It consisted of an oxygenator system with eight stationary meshes (◘ Figure 1) and multiple roller



◘ **Figure 1:** This mesh oxygenator, developed by John Gibbon and engineers from IBM, was for the first time used on May 6, 1953, in the first successful total cardiopulmonary bypass surgery. (Figure from: Malmros GVA et al. Oxygenation unit for extracorporeal devices. U.S. Patent 2,792,002 dated May 14, 1957).

pumps. Due to inadequate anticoagulation, however, clots formed on some of the meshes of the oxygenator, leading to a disruption of the blood layer and ensuing reduction in gas exchange. Nevertheless, the patient survived the operation.

Surface hypothermia

Although Gibbon was the first to successfully use a heart-lung machine during occlusion surgery of an atrial septal defect, his was not the first attempt to close the atrial septum. A short while prior to Gibbon's success, operations without the use of a heart-lung machine were considered an extraordinarily risky procedure. In the late 1940s, Wilfried Bigelow (Toronto) demonstrated in experimental studies that with a decrease in body temperature and the ensuing reduced metabolism, circulatory arrest, which under normothermia can only be tolerated by the central nervous system for approximately three minutes, could be significantly prolonged [8] . He concluded that using extremely cold temperatures to extend circulatory arrest time would be sufficient to allow for very rapid open heart surgeries. On September 2, 1952, Floyd John Lewis (Minneapolis) for the first time repaired an atrial septal defect in a 5-year-old girl under hypothermic conditions [9]. The patient was cooled to 28°C by the use of a cooling mat and, after successful surgery, rewarmed in a warm water bath. She was discharged from the hospital eleven days after the intervention.

Several research groups working at other hospitals, such as the groups of Henry Swan (Denver) and Charles Bailey (Philadelphia), have also reported successful atrial septal defect surgeries shortly afterwards. Even smaller surgical interventions to repair aortic valves and pulmonary valves have been done using this procedure. Since atrial septal defects could, in principle, also be repaired using surface hypothermia, Gibbons's achievement did not initially provoke any great enthusiasm. Furthermore, he was not able to replicate his success before abandoning this field of activity.

Cross-circulation

After the one successful surgery by Gibbon, open heart surgeries with use of the heart-lung machine were attempted across the world, but unfortunately with a low success rate. Although experimental animal surgeries with cardiopulmonary bypass have often been successful, humans did not seem to be able to survive this type of surgery. At that time, C. Walton Lillehei (Minneapolis) developed a modified procedure to allow for the use of cardiopulmonary bypass during cardiac surgery. With the help of the so-called cross-circulation technique, which other researchers reported in corresponding experimental attempts much earlier, the research group of Lillehei, on March 26, 1954, managed to maintain extracorporeal circulation using the lung function of a second person with the same blood group by means of corresponding cannulation and the use of a blood pump [10]. Venous blood from the patient was directed to the venous vascular system of the second person by means of a pump and, at the same time, the corresponding amount of arterialized blood from the donor was redirected to the patient by means of a pump. This way, blood circulation of the patient could be maintained while the patient's own heart was not able to exert its pump function due to the surgery. With this technique, the donor has not only taken over the respiratory work but also corrected any deviations of the patient's acid-base balance. Several years before , Anthony Andreasen and Frank Watson (London), during their preparatory work for this technique, found that dogs were able to survive experimental perfusions with a very low pump volume of as low as approximately 10 % of the normal cardiac output [11]. Approximately 10% of cardiac output had been supplied to the heart through the azygos vein, while both venae cavae had been occluded. This method, called the “azygos flow” principle, had then been adopted by several working groups. Such a low perfusion flow accommodated the limited capability of those early artificial oxygenators. During open heart surgery, the low perfusion flow also allowed for a better view of the surgical field due to the concomitantly reduced collateral blood flow.

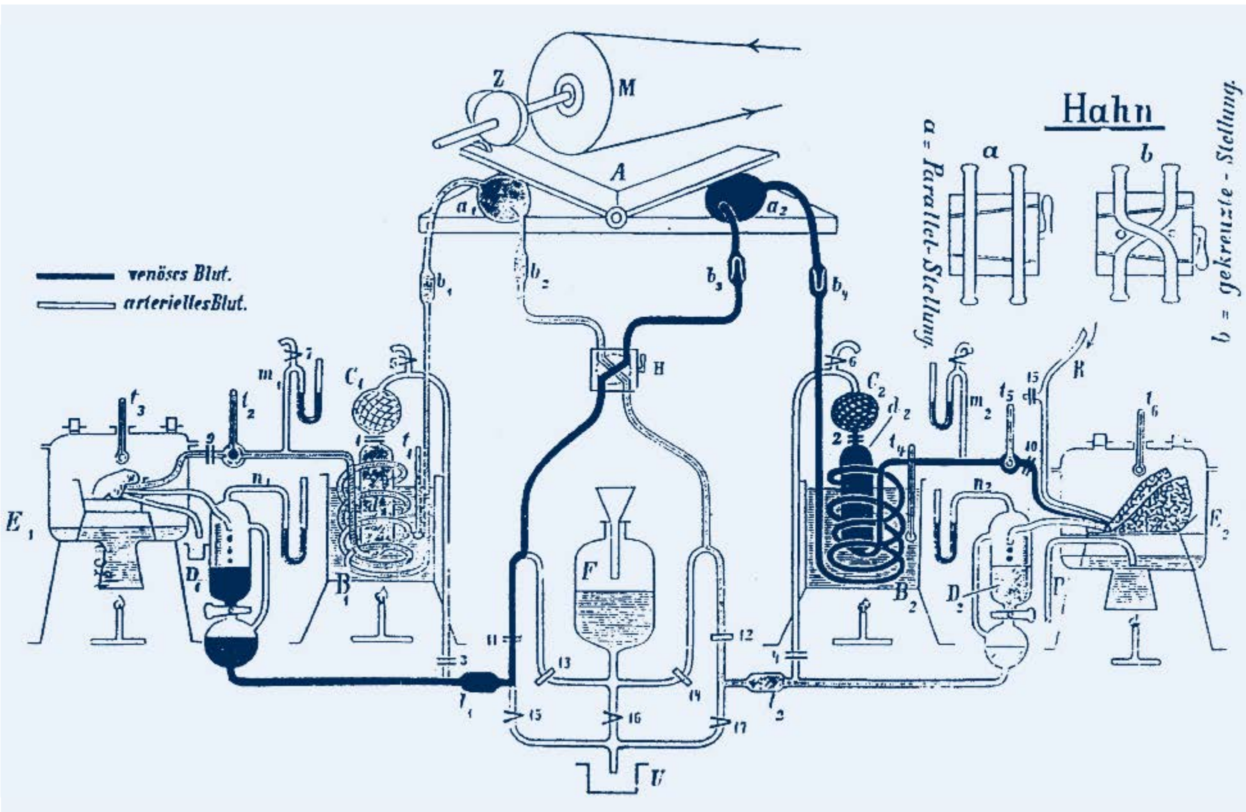
Until July 19, 1955, Lillehei was able to use this cross-circulation procedure in a total of 45 patients [12]. Most commonly, the blood circulation of the patient was connected to a blood group identical parent. When no suitable parent was available, however, there were also volunteers who were willing to help. With this method, Lillehei was able to carry out the first clinical series of open heart surgeries. In addition to ventricle septum defect closures, he also managed to perform more complex interventions such as the first repair of a Tetralogy of Fallot or an atrioventricular septal defect repair. This series of surgeries was extraordinarily successful. After 30 years, 22 patients out of a series of 45 patients were still alive despite a theoretical mortality risk of 200% both for the patients and the donors. Lillehei abandoned this method to start using a heart-lung machine developed by his own working group.

Alternative methods

Starting from March 3, 1955 and before moving on to using the artificial oxygenator, Lillehei operated on five very young patients whose circulation during heart surgery was maintained by perfusion with previously arterialized blood from a reservoir [13]. This method was similar to the very first procedures that had been developed in the mid-19th century to experimentally perfuse isolated organs. Subsequently, in the second half of the 19th century, these blood reservoirs were pressurized to reduce the required filling volume by means of shorter tubing [14-16]. Nearly a hundred years later, Lillehei did not extract blood from the donor's artery but he arterialized the venous blood. Immediately prior to blood donation, the donor limb where blood was to be collected was warmed, thus achieving a sufficiently high degree of oxygenation. This method allowed the oxygen saturation of the arterialized venous blood to increase from 29% to 94% [13].

Lillehei operated on another 15 patients who were too old to undergo the cross-circulation procedure and used a modified method of extracorporeal circulation instead. In this technique, gas exchange during cardiopulmonary bypass was done using excised animal lungs [17]. This gas exchange procedure had been developed back in 1895 by Carl Jacobj for his experimental organ perfusions (◘ Figure 2) [18]. Five years before, around 1890, Jacobj worked with the bubble oxygenation method, similar to the method presented by Schröder in 1882. Jacobj was searching for another method to "achieve arterialization of the blood in a way corresponding to natural arterialization in order to maximally exclude any damage to the blood or impairment of the substances added to the blood that could be caused by direct exposure to air [18]." On January 17, 1952, William Thornton Mustard (Toronto) used the bubble oxygenator in a human patient for the first time and that initial surgery was followed by six more. Mustard attempted surgical transposition of the large vessels but none of the seven severely ill patients survived this first series of surgeries [19]. In Mustard's subsequent series using excised lungs of monkeys, three patients survived. Prior to the procedure, blood residue had been removed from the three isolated lungs. The perfusion of these biological oxygenators, however, often led to edematous alterations in the isolated lungs with ensuing functional deterioration. Nevertheless, Lillehei was able to report five long-term survivors after operations using dog lungs for gas exchange.

Lillehei and Mustard were not the only ones experimenting with alternative methods. Dodrill had already perfused the patient's own lung with his pump during heart surgery with extracorporeal circulation. Dodrill had initially done temporary replacement of either the left or the right ventricle in order to operate on the corresponding heart valve. Subsequently, he also did simultaneous replacement of both ventricles with one pump each in order to perform open heart surgery while gas exchange was taking place via the patient's own lungs. A similar principle of extracorporeal circulation, a double-lung system, was also presented by Charles Drew (London) in 1959 [20]. Drew combined this method of extracorporeal circulation

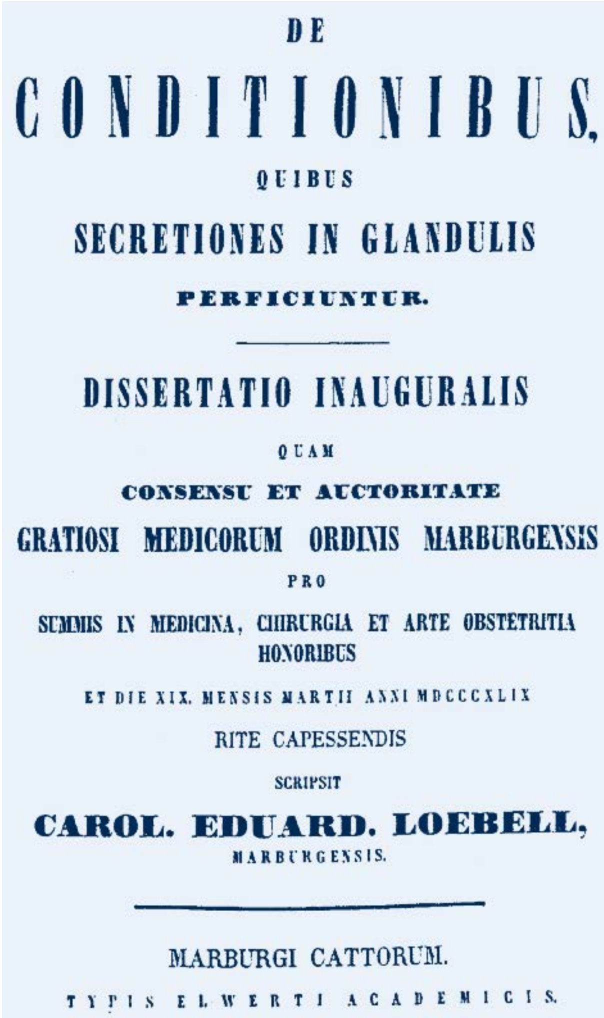


◘ **Figure 2:** First extracorporeal gas exchange with an excised lung. Jacobj's "Double hematisator" (1895) had to perfuse two organs: not only the target organ E1 (left side) but also the isolated lung E2 (right side), which necessitated a double pump system (top center). (Figure retrieved from 18).

with deep hypothermia as protection for circulatory arrest during the surgery.

Bubble oxygenation

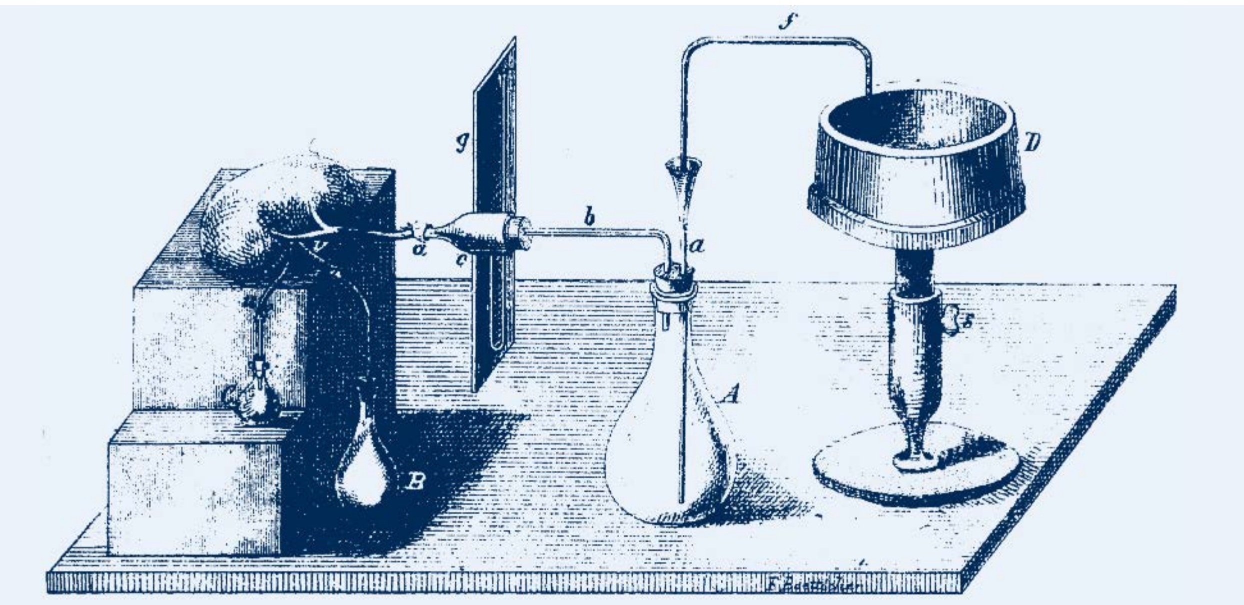
The heart-lung machine, which was developed by Richard DeWall in Lillehei's working group, consisted of a bubble oxygenator and the so-called "finger pumps" made by Sigmamotor Inc. The finger-pumps were the blood pumps previously used for cross-circulation [21]. In principle, this method of arterialization through direct insufflation of gas into the blood had already been presented in 1882 by Waldemar von Schröder [22]. Schröder had also been the first to enable extracorporeal artificial gas exchange of blood with the help of a special, customized device. He was the first to bring ambient air into direct contact with blood. In the following year, 1883, Abeles used pure oxygen [23]. Previously, researchers such as Loebell (◘ Figure 3), Bidder (◘ Figure 4), Brown-Sequard, Ludwig and Schmidt, and Bunge and Schmiedeberg performed the earliest perfusion experiments using oxygen-enriched venous blood (shaken with ambient air) or with naturally oxygenated blood extracted from the arterial vascular system of another experimental animal [14, 16, 24-26, 27, 28]. In 1890, Jacobj integrated a bubble oxygenator in his first perfusion device, the so-called "hematizer" (◘ Figure 5) [29]. The principle of bubble oxygenation could not be used in clinical practice for more than half a century due to the fact that the gas bubbles injected in the blood could not be fully eliminated after the gas exchange, which lead to arterial embolization.


DE
CONDITIONIBUS,
QUIBUS
SECRETIONES IN GLANDULIS
PERFICIUNTUR.

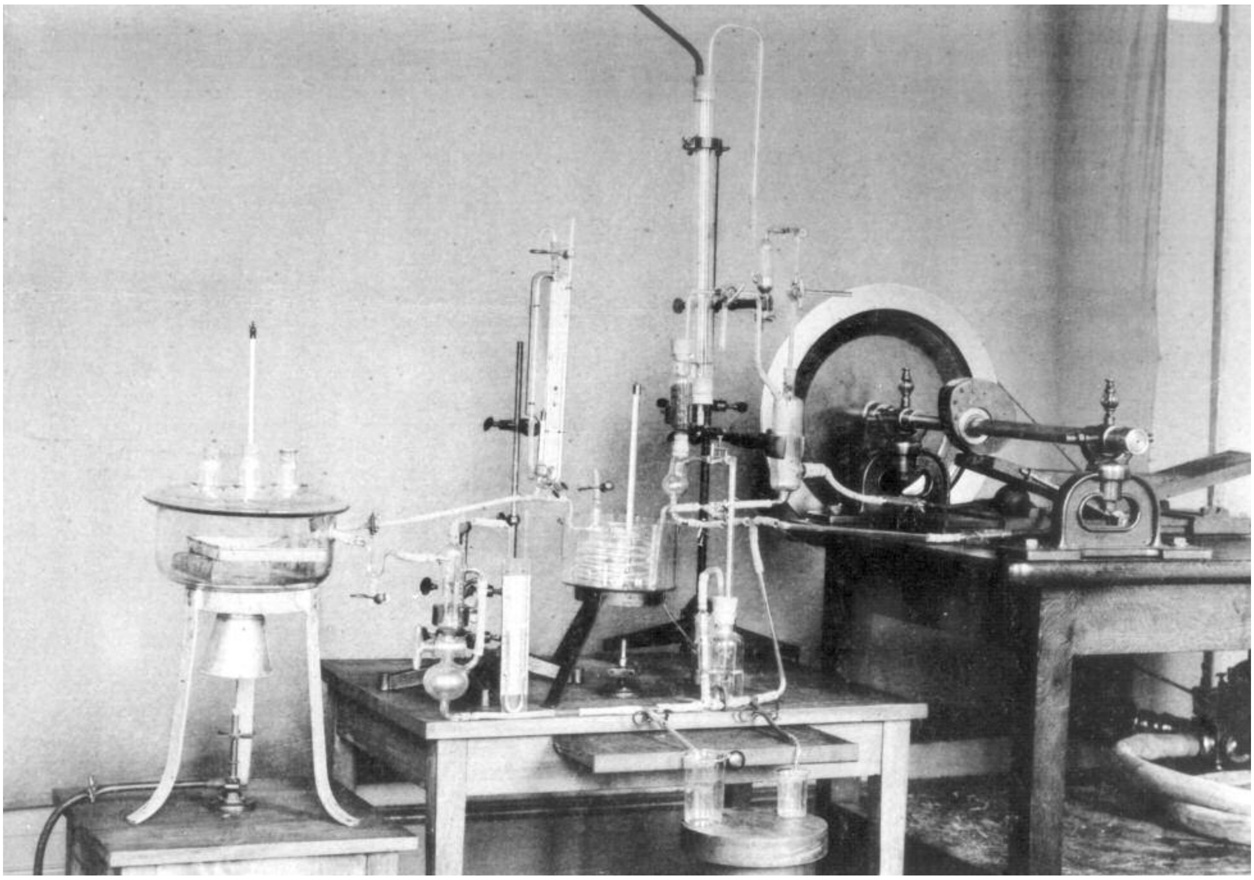
DISSERTATIO INAUGURALIS
QUAM
CONSENSU ET AUCTORITATE
GRATIOSI MEDICORUM ORDINIS MARBURGENSIS
PRO
SUMMIS IN MEDICINA, CHIRURGIA ET ARTE OBSTETRITIA HONORIBUS
ET DIE XIX. MENSIS MARTII ANNI MDCCCXLIX
RITE CAPESSENDIS
SCRIPSIT
CAROL. EDUARD. LOEBELL,
MARBURGENSIS.

MARBURGI CATTORUM.
TYPIS ELWERTI ACADEMICIS.

◘ **Figure 3:** Title page of the Doctoral thesis of Carl Eduard Loebell from 1849. He for the first time described perfusion of an organ: an isolated kidney. (Figure retrieved from 15).



◘ **Figure 4:** Probably the first illustration of a perfusion apparatus from the Doctoral thesis of Ernst Bidder (1862). The mercury column (a) was filled from the height-adjustable (S) mercury container (D) by means of siphon drain (f). Thereby, variable pressure was applied to the perfusate container (A) allowing to perfuse the isolated organ after passing a pressure gauge (g). (Figure retrieved from 14).



◘ **Figure 5:** Probably the first photograph of an extracorporeal circulation by Jacobj (1890). The pulsatile pump system was composed of a rubber balloon rhythmically compressed by a motor-driven spring-type rocker (right side). Gas exchange took place in a system with direct blood-air contact (center of image). As a precursor of today's heat exchanger, a glass spiral immersed in tempered water was used to heat the blood. (Figure retrieved from 29).

It was only with the introduction of the de-foaming of blood by means of silicone components by Clark, Gollan and Gupta (Yellow Springs) in 1950 that bubble oxygenation was implemented in clinical practice [30]. Blood was exposed to direct contact with oxygen in the oxygenator developed by DeWall-Lillehei and then de-foamed by contact with silicone components in a helical spiral consisting of plastic tubing. Compared to the very expensive Gibbon machine, this oxygenation system was inexpensive and easy to manufacture. Consequently, following the first use of the DeWall oxygenator on May 13, 1955 in Minneapolis, there was an increase in open heart surgery all over the world.

Film oxygenation

Film oxygenation was being devised, parallel to the very successful bubble oxygenation, to enable prolonged perfusion periods. Gibbon's heart-lung machine included a film oxygenator consisting of several stationary grids. Blood flowed down these metal grids exposing it to an oxygenic atmosphere. After the first successful use, and also some failed attempts, this oxygenation system was improved, refined and, finally, implemented at the nearby Mayo Clinic in Rochester [31]. There were four survivors out of the eight patients operated on by John Kirklin and his working group on March 22, 1955. This was the first relatively successful series of operations with a heart-lung machine.

Denis Melrose (London) developed a film oxygenator that was implemented all over the world [32]. He was one of the first to report successful aortic valve surgery on December 9, 1953 [33]. Another famous refinement was introduced by Earle Kay and Frederick Cross (Cleveland, Ohio) in 1956: vertically rotating discs. The rotating-disc oxygenator by Kay-Cross was being used in many centers until the 1970s [34]. Max von Frey and Max Gruber (Leipzig, Germany) had presented the basics of the film oxygenation principle back in 1885 (◘ Figure 6). In the world's first closed perfusion circuit, they had integrated a rotating cylinder. On its inner wall the blood was spread in an oxygenic atmosphere [35]. Before the presentation of this first precursor to today's heart-lung machine, it was not possible to perform prolonged continuous perfusion experiments. Such perfusion experiments had to be interrupted again and again to refill the reservoir with new oxygen-rich perfusate. Only the development of the closed perfusion circuit solved this problem. The oxygenation principle of creating a blood film within an oxygenic atmosphere (blood in gas), in contrast to the insufflation of oxygen into the blood (gas in blood), was then improved and refined by a number of other researchers [36-40]. Similar to the method by Frey and Gruber, in Gibbon's first oxygenators from the 1930s blood was also flowing down within cylinders in an oxygenic atmosphere [41-43]. In earlier versions of film oxygenators developed by other researchers, blood was running down textile fabrics or glass panels in an oxygenic atmosphere. As an alternative, the surface of the blood was enlarged by the use of glass beads or the blood was spread over an inverted bell [40, 44-46]. For large-scale exposure of blood to oxygen, rotating discs were used in an earlier version. Horizontally rotating discs were more likely to be used to spread blood over larger surfaces by means of centrifugal force [47]. In Stockholm, in 1946, Clarence Crafoord and Andersson constructed the first "rotating disc" oxygenator. A disc oxygenator with vertically rotating discs was introduced by Viking Olov Björk in 1948 for isolated perfusion of the brain during experimental heart surgery [48].

Isolated perfusion of the head

The idea of using artificial perfusion in connection with cardiac and vascular operations was presented by Zeller (Berlin, Germany) back in 1908 [49]. He envisioned the use of a perfusion apparatus for circulatory support during surgeries such as a cardiac stab injury that Rehn had successfully operated on a few years prior, or a pulmonary embolectomy like the one Trendelenburg was able to perform successfully (in animal experiments) [15]. In principle, the idea of maintaining life or restoring life by replacing pump function of the heart and possibly arterializing blood by artificial means, had already been described in 1812 by César Julien-Jean Le Gallois [50]. Around 150 years ago, Eduard Brown-Sequardt for the first time described the artificial perfusion of the head in decapitated criminals without having in mind a relationship with heart surgery [24]. In the 1930s, Laurence O'Shaughnessy presented his concept of the future of heart surgery. He believed that open heart surgery would only be possible if at least the brain of the patient was per-

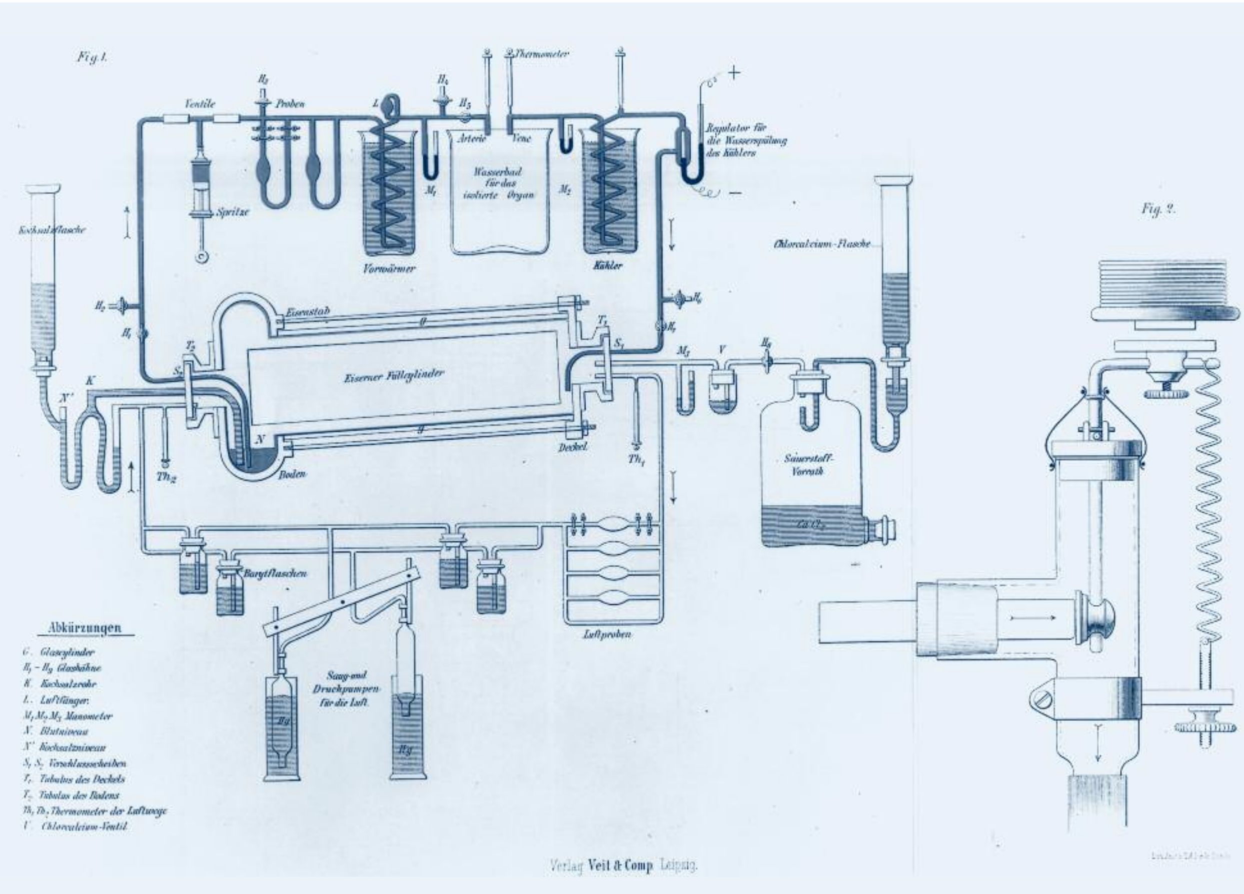
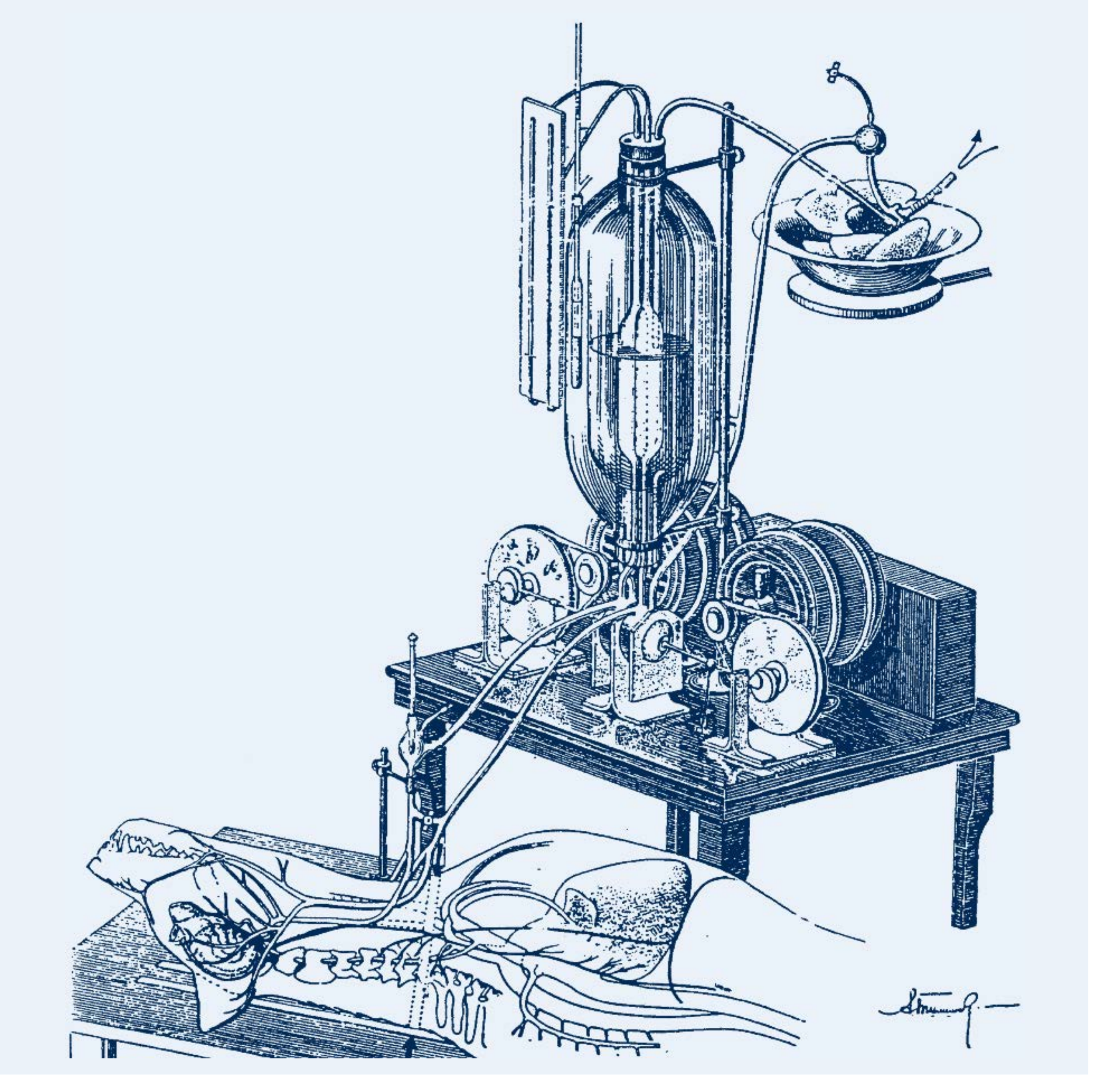


Figure 6: The "respiration apparatus" by von Frey and Gruber (1885) is usually referred to as a precursor of today's heart-lung machine. The first film oxygenator "Eiserner Füllzylinder" (G) was integrated into a first-time closed extracorporeal perfusion circuit. Perfusion was maintained by a motor-driven syringe. The perfusate was rewarmed prior to perfusion and cooled down after passage through the organ. An air trap (L) was used to protect the organ from embolization (5). Temperature and pressure were measured and sampling ports were provided. (Figure retrieved from 35).

fused artificially while the heart was not able to exert its pump function [51]. In the Soviet Union, however, one of the great pioneers of extracorporeal circulation, Sergej Bryuchonenko, had already done experimental studies in isolated perfusion of dog heads back in the early 1920s (◘ Figure 7). He had constructed a heart-lung machine which, after continuous refinement, also allowed for perfusion of the animal's entire organism. As early as in 1928, Bryuchonenko proposed the possible application of his perfusion method in connection with human heart surgery. Later, Nikolai Terebinski was able, with the apparatus of Bryuchonenko, the so-called "autojector", to perform experimental open heart surgery in the 1930s [52].

Due to the limited gas exchange capacity of the early artificial oxygenators, in the 1940s a number of working groups still thought that only the brain, as the most vulnerable organ, should be perfused during cardiac surgery. It was presumed that other organs would tolerate ischemic periods lasting thirty minutes without being harmed. It was only with an increasing efficiency of the oxygenators that systemic perfusion of the entire organism was attempted just as Gibbon had intended at the beginning of his research efforts in the 1930s. It was after the death of a female patient following pulmonary embolectomy on October 3, 1930, that Gibbon started wondering whether the function of heart and lungs could be replaced artificially for such an intervention.

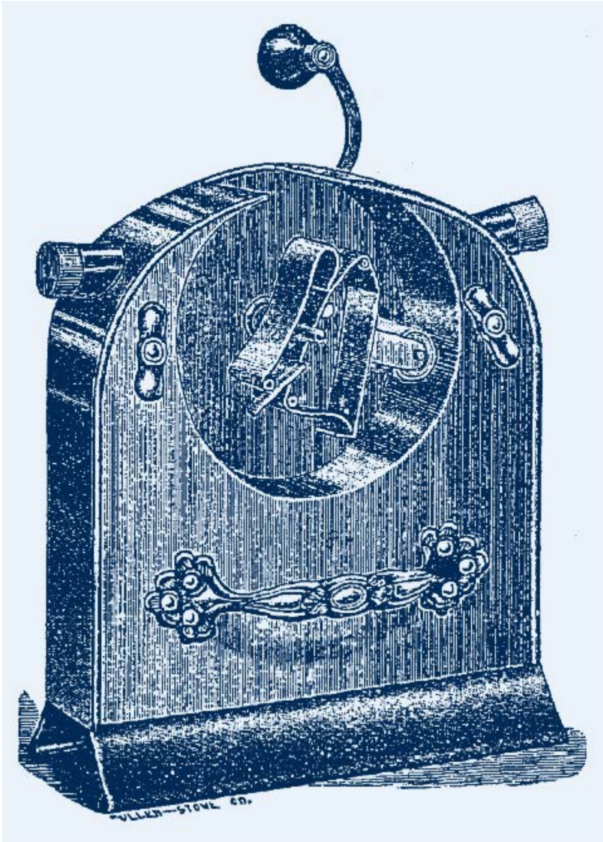


◘ **Figure 7:** Brukhonenko, in the 1920s, perfused dog heads with his "autojector". A double membrane pump system pumped the venous blood through the excised ventilated lung and the arterialized blood back into the carotids of the experimental animal. In doing so, reactions to external stimuli could be maintained for up to 3.5 hours. (Figure retrieved from: Brukhonenko SS, Tchechulin SI, Experiments on isolation of dog's head (russ.). Trudy Nauchnogo Khimiko-Farmatsev. Inst. 1928; 20, (265): 7-43.)

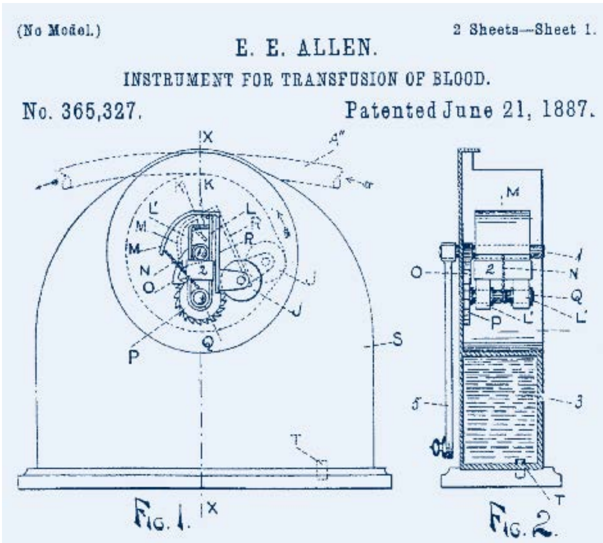
Blood pumps

In the 1930s, Gibbon integrated a modified Dale-Schuster pump in his first perfusion apparatus [41]. This pulsatile membrane pump had been presented in 1928 and subsequently used in numerous modifications of perfusion devices [53]. Prior to the introduction of this type of membrane pumps, syringe or piston pumps were incorporated into the early artificial circulation devices which were often driven by motors [45, 54-59]. In Jacobj's perfusion apparatus from 1890, pulsatile flow characteristics could be generated by the rhythmically compressed rubber balloon [29]. Porter and Bradley had the non-pulsatile functioning roller pump patented as early as April 17, 1855. Shortly thereafter, this type of pump was proposed by Allen for the transport of blood in the context of transfusion despite the fact that blood groups were only detected some years later by Landsteiner (◘ Figure 8, 9) [60]. A double roller pump, which is still being used today, was developed by Charles Truax in 1891. At that time, the device still needed to be operated by hand crank (◘ Figure 10). In 1927, the roller pump was incorporated into an artificial perfusion apparatus by Issekutz for gas transport only [61]. Fleisch used the roller pump in 1935 for the transport of blood for experimental perfusion of isolated organs [62]. At about the same time, it was also being used by Georg Haas (Giessen, Germany) in his first artificial kidneys [63]. Haas decided to use a special type of roller pump which had been presented by Alfred Beck (Kiel, Germany) for blood transfusion in 1924 and 1925 and which became famous as "Beck'sche Mühle" [Beck's mill] [64, 65].

Due to the many advantages, such as the measurable and controllable perfusion flow, the fact that valves were not needed for the directed blood stream, easy cleaning as blood contact is limited to the inside of the tubing, roller pumps were used in Gibbon's developing heart-lung machine since 1939 [42]. It was Michael E. DeBakey (Tulane) who had proposed to Gibbon to use roller pumps in his perfusion apparatus and brought him a model of his pump that he had patented in 1934. Since then, the roller pump has always been associated with DeBakey's name [66, 67]. The roller pump prevailed despite its non-pulsatile flow characteristics and still represents the most common type of pump for extracorporeal circulation with heart-lung machines and dialysis devices. It is only in recent years that the centrifugal pump had been developed as an alternative to the roller pump. As a matter of fact, a centrifugal pump was patented already in 1901. The development of this type of pump for the transport of blood in the circulation, however, only began in the 1960s by George Saxton and Charles Andrews (Illinois) [68]. At that time, the original aim was to construct an artificial heart with a magnetic drive allowing for transcutaneous application. Soon afterwards, however, the centrifugal pump was also



◘ **Figure 8:** Woodcut of the early Allen pump (1887) as "The Surgeons Pump". Its field of application was blood transfusion although blood groups were only discovered a few years later. (Figure retrieved from: Herdmann WJ. The surgeons pump. JAMA 1887; 9:59-60).



◘ **Figure 9:** Patent document of the first roller pump by Allen (1887). It was designed for pumping blood and it only consisted of one roller (J) and was operated by means of a hand crank (5). A reservoir for warm water (3) was closed with a cork (T). (Figure retrieved from: Allen EE. Instrument for transfusion of blood. U.S. Patent No. 365,327 dated June 21, 1887).

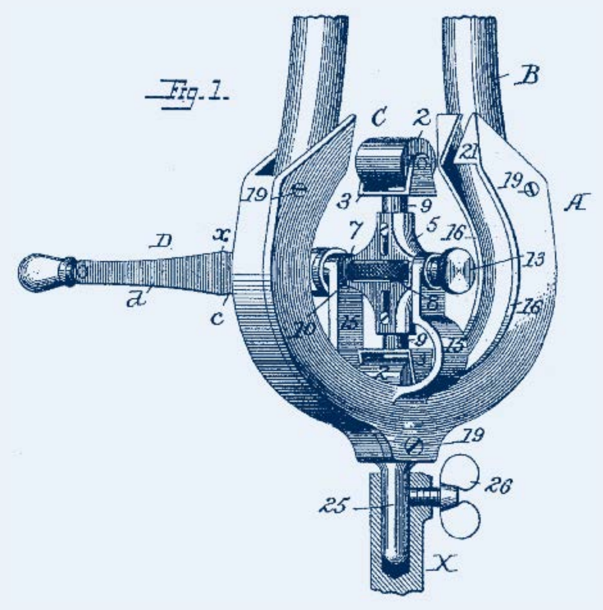


Figure 10: First double roller pump according to Truax (Patented in 1891). (Figure retrieved from: Truax CH. Surgical pump. U.S. Patent No. 487,136 dated November 29, 1892).

suggested for use in the heart-lung machine. At present, the centrifugal pump is replacing the roller pump as an arterial pump in a number of centers.

Filtration of the blood

As early as 1915, particulate embolization and infarcts in isolated perfused organs were demonstrated with the use of linen tissue for artificial gas exchange [45]. By 1948, Björk had also attributed the cause of death of experimental animals during his perfusion experiments to arterial embolization. In 1950, Gibbon detected embolization in animals that died in a coma without any reflexes after undergoing artificial perfusion. The use of blood filters increased survival rates of experimental animals [69]. The priming of the heart-lung machine with donor blood then resulted in another application of filtration systems. Swank developed filter systems using Dacron wool to remove micro aggregates. Today, filter systems are an integral part of the extracorporeal system of heart-lung machines and, along with the introduction of membrane oxygenators, they are considered to be one of the major measures to reduce neurological complications associated with cardiopulmonary bypass.

Membrane oxygenators

At the beginning of their introduction in the late 1950s, membrane oxygenators were found to be more difficult to de-air, suffered from leakage, and showed insufficient gas exchange capacity. In general, membrane oxygenators were significantly more difficult to operate than bubble oxygenators but the basic advantage of this method of gas exchange was evident. The blood was completely separated from the gaseous phase by a membrane, which served to eliminate the problems resulting from the direct contact of blood to gas. In 1943, while developing hemodialysis, Willem Kolff (Kampen, The Netherlands) observed that blood had taken up oxygen through a membrane since the blood had turned bright red after passing through his dialyzers [70]. In the mid-fifties, Kolff addressed the problem of membrane oxygenation and developed the first prototype in Cleveland [71] . Other researchers followed this path and were then able to embark on the first clinical applications [72]. In the 1960s, the first commercially available membrane oxygenators were successfully used, especially for prolonged perfusions. In the following decade, it became possible to maintain perfusions for days and later even for weeks to compensate for respiratory problems, as well in the context of mechanical circulatory assist. In recent years, nearly all other oxygenation strategies have been abandoned in favor of membrane oxygenation. The new developments of capillary hollow fiber oxygenators have been found to be superior in a number of tests investigating the organ function of patients after use of cardiopulmonary bypass.

Hemodilution

With the introduction of hemodilution for perfusion at the end of the 1950s, further progress was made toward maintaining postoperative organ function, especially with respect to the lungs and the kidneys. This led to abandoning the procedure of priming the extracorporeal circuit with donor blood. Even Gibbon, in his first experimental animals, had renounced the filling of the extracorporeal circuit with blood. Melrose also had not filled the heart-lung machine with blood when performing his animal experiments. The clinical use of hemodilution for perfusion was reported by Zuhdi, Panico and Neptune in the late 1950s. Along with the altered rheology with improved micro circulation, the organizational problem of donor blood supply could also be reduced significantly. This approach furthermore allowed emergency interventions to occur with a rapidly filled and de-aired heart-lung machine. It was recognized that the use of hemodilution for perfusion would result in a lower number of oxygen carriers but this could be partly offset by hypothermia.

Perfusion hypothermia

In addition to surface hypothermia induced by ice water baths or by means of cooling mats, systemic hypothermia was also recognized as a method to be used with extracorporeal circulation. Initially, extracorporeal perfusion systems were used without oxygenation systems for this pupose. Compared to surface cooling, perfusion hypothermia allowed for a more homogeneous cooling without major temperature gradients. In 1952, Edmund Joseph Delorme (Edinburgh), reported on his method of hypothermia induction by means of blood stream cooling, where blood circulated through a cooling system outside the body [73]. He cooled arterial blood before returning it into a peripheral vein. Ite Boerema (Amsterdam)

Timetable of extracorporeal circulation

1812	César Julien Jean LeGallois [50]	Idea: artificial heart function, oxygenation
1828	James Phillips Kay [26]	Injections of arterial blood
1849	Carol. Eduard. Loebell [16]	Isolated renal perfusion
1858	Eduard Brown-Sequard [24]	Limb perfusion of hanged persons
1862	Ernst Bidder [14]	Isolated renal perfusion
1867	Alexander Schmidt [28]	Isolated renal perfusion
1868	Wilhelm Ludwig, Alexander Schmidt [27]	Shaking with atmospheric air
1877	G. Bunge and O. Schmiedeberg [25]	Shaking with atmospheric air
1882	Waldemar von Schröder [22].	Bubble oxygenation
1883	M. Abeles [23]	Bubble oxygenation with oxygen
1884	Max von Frey, Max Gruber [35]	Film oxygenator, closed circuit
1890	Carl Jacobj [29]	Hematisator
1895	Carl Jacobj [18]	Double hematisator, isolated lung
1903	T. G. Brodie [90]	Piston pump with blood-air mixture
1907	Johannes Bock [91]	Motor-driven double syringe
1908	O. Zeller [49]	Idea: heart-lung machine for surgery
1908	K. Skutul [92]	Overview of perfusion devices
1915	A. N. Richards, Cecil K. Drinker [45]	Textile film oxygenation
1915	Donal Russel Hooker [40]	Rubber disc film oxygenation
1926	A. Bornstein [44]	Glass bead film oxygenation
1927	Sergej Bryuchonenko, S. Tchetchuline [52]	Head perfusion with "autojector"
1928	H. H. Dale, E. H. J. Schuster [53]	Membrane pumps
1928	Bayliss, Fee and Ogden [37]	Film oxygenation with rotating cones
1932	U. S. von Euler and C. Heymans [93]	Spray oxygenator
1933	I. de Burgh Daly and W. V. Thorpe [39]	Film oxygenation with ebony discs
1934	E. W. H. Cruickshank[38]	Magnetic drive of a film oxygenator
1934	C. Lovatt Evans, F. Grande and F. Hsu [47]	Vertical cylindrical film oxygenator
1935	Alfred Fleisch [62]	Roller pump in perfusion apparatus
1935	Alexis Carrel, Charles Lindbergh [94]	Perfusion system for isolated organs
3.10.1930	John Heysham Gibbon jr. [95]	Death of his patient and idea of CPB
1937	John Heysham Gibbon jr. [41]	First report on perfusion experiments
1939	Laurence O'Shaughnessy [51]	Head perfusion for heart surgery
1940	Herbert Schwiegk [96].	Apparatus for resuscitation
1948	Viking Olov Björk [48]	Disc oxygenator for head perfusion
1949	J. Jongbloed [97]	Effective spiral oxygenator
1950	L. Clark, F. Gollan, V. Gupta [30]	Silicone defoaming bubble oxygenator
9.8.1951	Achille Mario Dogliotti, A. Constantini [1]	Successful partial bypass
5.4.1951	Clarence Dennis [98, 3].	Total cardiopulmonary bypass
3.7.1952	Forest Dewey Dodrill [4]	Mitral valve surgery with left-heart bypass
21.10.1952	Forest Dewey Dodrill [5]	Pulmonary valve surgery with right-heart bypass
6.5. 1953	John Heysham Gibbon jr [7]	Successful cardiopulmonary bypass

described a similar procedure in 1951 [74]. During his stay at Crafoord in Stockholm, more precisely in 1952, André A. Juvenelle developed a concept that combined extracorporeal circulation with hypothermia [75]. He used the device which had been developed by Crafoord and described by Björk to deliver perfusion and an ice water bath to induce hypothermia. In 1956, Brown, Sealy and Young (Durham, NC) combined the DeWall-Lillehei oxygenator with a heat exchanger for induction of hypothermia during intracardiac surgery [76]. Following this initial collaboration, they developed the "Brown-Harrison" heat exchanger which was used all over the world. The combination of cardiopulmonary bypass and perfusion hypothermia led to increased safety and prolonged ischemia time of the myocardium. In the late 1960s, extracorporeal circulation was only combined with surface cooling or warming for the purpose of cooling or rewarming. Such pioneering work was first reported by Hikasa (Kyoto, Japan) and was only later adopted by others. In the early 1970s, Brian Barratt-Boyes (Auckland, New Zealand) combined surface hypothermia with rewarming and the use of the heart-lung machine. On July 16, 1954, during the first European surgery, Clarence Crafoord and Ake Senning (Stockholm) had cooled the patient with surface hypothermia before applying the heart-lung machine. The patient was then also rewarmed without extracorporeal circulation.

Today, heart-lung machines are more efficient and prime volumes are smaller. Moreover, surgeries are being increasingly performed with normothermia. This trend has also been supported by the further refinement of myocardial protective techniques.

Timetable of cardiovascular surgery

September 9,1896	Ludwig Rehn	First successful heart suture
1913	Ludwig Rehn, Ferdinand Sauerbruch	Pericardectomy
1910	Alexis Carrel	Vascular suture technique
May 20, 1923	Elliott Cutler, Samuel Levine	Valvotomy for mitral stenosis
May 6, 1925	Henry S. Souttar	Mitral valve commissurotomy
March 18, 1924	Martin Kirschner	Lung embolectomy
1931	Ferdinand Sauerbruch	Ventricular aneurysm resection
August 26, 1938	Robert Edward Gross	Ductus ligature
October 19, 1944	Clarence Crafoord	ISTA repair
November 29, 1944	Alfred Blalock	Blalock-Taussig shunt
December 4, 1947	Thomas Holmes Sellors	Pulmonary stenosis dilatation
February 16, 1948	Russel Claude Brock	Pulmonary valve valvotomy
June 10, 1948	Charles Philamore Bailey	Mitral valve commissurotomy
June 16, 1948	Dwight Emary Harken	Mitral valve commissurotomy
September 2, 1952	Floyd John Lewis	Atrial septum closure
September 11, 1952	Charles Hufnagel	Aortic valve replacement (descendens)
May 6, 1953	John Heysham Gibbon jr	ASD closure with CBP
March 26, 1954	Clarence Walton Lillehei	VSD closure with cross-circulation
August 31, 1954	Clarence Walton Lillehei	ToF repair
March 22, 1955	John Webster Kirklin	VSD closure with CBP
March 10, 1960	Dwight E. Harken	Aortic valve replacement
September 21, 1960	Albert Starr	Mitral valve replacement
May 2, 1960	Robert H. Goetz	A. mammaria bypass
July 24, 1962	Donald Nixon Ross	Homograft aortic valve replacement
April 5, 1962	David Coston Sabiston	Coronary vein bypass
June 11, 1963	James Daniel Hardy	Lung transplantation
January 23, 1964	James Daniel Hardy	Monkey heart transplantation in a human
December 2/3, 1967	Christiaan Neethling Barnard	Heart transplantation
December 24, 1969	Clarence Walton Lillehei	Heart-lung transplantation
May 4, 1975	Adib Domingo Jatene	Arterial switch operation in TGA
March 9, 1981	Bruce A. Reitz	Heart-lung transplantation

Myocardial protection and cardioplegia

From the beginning of open heart surgery, researchers have been developing methods which would protect the heart from ischemic injury. Initially, surgeries were performed with a beating, continuously perfused or a fibrillating heart.

Inspired by the observations made by Sydney Ringer (1883) and Donald Russel Hooker (1929) on the influence of electrolytes on cardiac action, some researchers developed cardioplegia that contained active solutions to provoke reversible cardiac arrest [77, 78]. Chemically induced cardiac arrest, later combined with topical hypothermia, was expected to drastically reduce myocardial oxygen consumption and allowed for the temporary interruption of coronary blood flow.

In the fall of 1952, Conrad Ramsay Lam (Detroit) started his work with cardioplegic solutions [79]. He discovered that an injection of potassium chloride solution into the left ventricle provoked cardiac arrest that could be reversed with reperfusion. In 1955, Melrose induced "elective" reversible cardiac arrest by injecting potassium citrate into the aortic root [80]. Using dog, cat and isolated rabbit hearts, he showed that the hearts could be arrested by means of potassium-containing solutions and that a subsequent recovery could be induced even after prolonged interruption of coronary perfusion. After Melrose had published his animal experiments, his potassium citrate cardioplegia method was adopted by Effler for clinical use. On February 17, 1956, Effler for the first time combined the interruption of coronary flow during a ventricular septal defect surgery on a 17-month-old child with artificial cardiac arrest induced by injecting potassium citrate solution into the proximal aorta [81].

At that time, it was also possible to induce a short cardioplegic arrest by injecting acetylcholine, which method was also developed by Lam [79, 82]. In 1958, Sealy developed a cardioplegic solution containing potassium, magnesium and procaine for selective cardiac arrest during hypothermia [83]. Clinical use of pharmacologically induced cardioplegia in heart surgery, however, ended in the late 1950s as reports were published on myocardial necrosis after potassium citrate-induced cardioplegia [84, 85]. Due to these reports, pharmacological cardiac arrest had been abandoned for the following 15 years in favor of beating and induced fibrillating hearts in connection with continuous, including retrograde, coronary perfusion or an intermittently perfused myocardium, as well as an ischemic topically cooled myocardium [86].

In Europe, several research groups continued developing solutions for safe chemical induction of cardioplegia, such as the German researchers Bretschneider (Köln, Göttingen) and Kirsch (Hamburg). David Hearse (London) then developed a crystalloid cardioplegia with potassium chloride that was used clinically by Braimbridge at the St. Thomas Hospital in 1975.

In the mid 1970s, William Gay and Paul Ebert (New York) provided for a slow revival of chemically induced cardioplegia in the USA [87]. They found that crystalloid cardioplegia solutions with moderate potassium concentrations can improve recovery of the heart after prolonged ischemia time. Later research by Tyers and Todd also showed the advantages of a solution with lower potassium concentration as compared to the Melrose solution [88].

The use of cold blood mixed with potassium chloride became popular by the end of the 1970s, especially due to the research efforts of Gerald Buckberg (Los Angeles) [89]. Since that time, blood has been widely used as a vehicle for cardioplegia and myocardial protective components due to its higher oxygen transport capacity and the natural buffering characteristics. The method of retrograde perfusion via the coronary sinus, already described by Lillehei in 1957, was also revived in the early 1980s in the context of blood cardioplegia. At the beginning of the 1990s, after the first reports by Lichtenstein (Toronto), normothermic blood cardioplegic methods were also increasingly preferred. The technique of normothermic blood cardioplegia was then simplified according to the Calafiore method. Nevertheless, the discussion of whether blood cardioplegia is preferable to crystalloid cardioplegia continues to this day. Furthermore, some centers achieve excellent results with the method of "intermittent cross-clamping".

Present times

Modern heart-lung machines show few differences compared to the devices used at the beginning of the cardiopulmonary bypass era. Although the methods for pumping blood and gas exchange have barely changed, they have been refined and modified. The function of the heart-lung machine, however, is extraordinarily reliable today and the control systems show high precision. Contemporary oxygenators allow for longer perfusion times than seen in the past. The priming volumes of extracorporeal systems have been reduced to such an extent that cardiopulmonary bypass surgery, even in selected neonatal patients, is feasible without transfusion of blood components. Further miniaturization of components is currently being explored.

In recent years, the focus has been on biocompatibility. A variety of coating systems are currently being used. Cardiotomy suction, which is associated with the harmful exposure of blood to air, has been identified as one of the major sources of hemolysis. Its use is now subject to more control and in some extracorporeal systems cardiotomy suction is completely avoided.

Over the past few decades, the number of cardiopulmonary bypass surgeries worldwide has consistently increased. Introduction of surgical coronary revascularization in the 1970's is one of the major reasons. However, coronary bypass surgery is increasingly being replaced by catheter interventional methods. At the same time, stents with increasingly more efficient coatings are available after appropriate dilatation of the stenotic vessel areas. Patients in need of surgical treatment of coronary heart disease are increasingly operated on without the use of a heart-lung machine (OPCAB).

The number of surgeries for repair of congenital lesions may also decrease as a result of the successful pediatric cardiology interventions. As prenatal diagnostics become more and more accurate, catheter-assisted septal occlusions and dilatations of stenosed heart valves and blood vessels decrease the number of children in need of cardiopulmonary bypass surgery.

Nevertheless, the use of the heart-lung machine will not become completely dispensable in the foreseeable future.

References

[1] Dogliotti AM, Constantini A. Primo caso di applicazione all´uomo di un apparecchio di circulazione sanguigna extracorporea. Minerva Chirurgica 1951; 6:657-659.

[2] Dogliotti AM, Del Poli G, Caldarola L. A cardiopulmonary machine for extracorporeal circulation of blood. Journal of the International College of Surgeons -1954; 22:107-114.

[3] Dennis C, Spring DS, Jr., Nelson GE, Karlson KE, Nelson RM, Thomas JV, Eder WP, Varco RL. Development of a pump-oxygenator to replace the heart and lungs; an apparatus applicable to human patients and application in one case. Annals of Surgery 1951; 134:709-721.

[4] Dodrill FD, Hill E, Gerisch RA. Temporary mechanical substitute for the left ventricle in man. J Am Med Assoc 1952; 150:642-4.

[5] Dodrill FD, Hill E, Gerisch RA, Johnson A. Pulmonary valvuloplasty under direct vision using the mechanical heart for a complete by-pass of the right heart in a patient with congenital pulmonary stenosis. J Thorac Surg 1953; 26:584-94; discussion 195-7.

[6] Böttcher W, Schäfer K. John Heysham Gibbon jr. (1903-1973). Kardiotechnik 2003; 12:78-80.

[7] Gibbon JH, Jr. Application of a mechanical heart and lung apparatus to cardiac surgery. Minnesota Medicine 1954; 37:171-187.

[8] Bigelow WG. Cold Hearts. The Story of Hypothermia and the Pacemaker in Heart Surgery. Toronto, Ontario: McClelland and Stewart Limited, 1984.

[9] Lewis FJ, Taufic M. Closure of atrial septal defects with the aid of hypothermia; experimental accomplishments and the report of one successful case. Surgery 1953; 33:52-59.

[10] Lillehei CW, Cohen M, Warden HE, Ziegler NR, Varco RL. Results of direct vision closure of ventricular septal defects in eight patients by means of controlled cross circulation. Surgery, Gynecology and Obstetrics 1955; 101:446-466.

[11] Andreasen AT, Watson F. Experimental cardiovascular surgery. "The azygos factor". British Journal of Surgery 1952; 39:548-551.

[12] Lillehei CW, Varco RL, Cohen M, Warden HE, Patton C, Moller JH. The first open-heart repairs of ventricular septal defect, atrioventricular communis, and tetralogy of Fallot using extracorporeal circulation by cross-circulation: a 30-year follow-up. Ann Thorac Surg 1986; 41:4-21.

[13] Lillehei CW, Cohen M, Warden HE, Read RC, DeWall RA, Aust JB, Varco RL. Direct vision intracardiac surgery. By means of controlled cross circulation or continuous arterial reservoir perfusion for correction of ventricular septal defects, atrioventricularis communis, isolated infundibular pulmonic stenosis and tetralogy of fallot. In: Lam CR, ed. Cardiovascular Surgery. Studies in Physiology, Diagnosis and Techniques (Proceedings of the Symposium held at Henry Ford Hospital, Detroit, Michigan; March, 1955). Philadelphia: W.B. Saunders, 1955:371-392.

[14] Bidder E. Beiträge zur Lehre von der Function der Niere. Inaugural-Dissertation Dorpat, 1862.

[15] Böttcher W, Alexi-Meskishvili V, Hetzer R. Geschichtliche Entwicklung der extrakorporalen Zirkulation. Isolierte Organperfusion im 19. Jahrhundert. Zeitschrift für Herz-, Thorax- und Gefäßchirurgie 2000; 14:93-99.

[16] Loebell CE. De conditionibus quibus secretiones in glandulis perficiuntur. Dissertatio Inauguralis Marburg, 1849.

[17] Campbell GS, Crisp NW, Brown EB, Jr. Total cardiac bypass in humans utilizing a pump and heterologous lung oxygenator (dog lungs). Surgery 1956; 40:364-371.

[18] Jacobj C. Ein Beitrag zur Technik der künstlichen Durchblutung überlebender Organe. Archiv für Experimentelle Pathologie und Pharmakologie 1895; 31:330-348.

[19] Mustard WT, Chute AL, Keith JD, Sirek A, Rowe RD, Vlad P. A surgical approach to transposition of the great vessels with extracorporeal circuit. Surgery 1954; 36:39-51.

[20] Drew CE, Keen G, Benazon DB. Profound hypothermia. Lancet 1959; 1:745-747.

[21] DeWall RA, Warden HE, Lillehei CW. The helix reservoir bubble oxygenator and its clinical application. In: Allen JG, ed. Extracorporeal circulation. Springfield, Ill.: Charles C. Thomas, 1958:41-56.

[22] von Schröder W. Ueber die Bildungsstätte des Harnstoffs. Archiv für experimentelle Pathologie und Pharmakologie 1882; 15:364-400.

[23] Abeles M. Über Secretion aus der überlebenden durchbluteten Niere. Sitzungsberichte der mathematisch-naturwissenschaftlichen Classe der kaiserlichen Akademie der Wissenschaften. Wien 1883; 87:187-198.

[24] Brown-Séquard E. Recherches expérimentales sur les propriétés physiologiques et les usages du sang rouge et du sang noir et de leurs principaux éléments gazeux, l´oxygène et l´acide carbonique. Journal de la Physiologie de l´Homme et des Animaux 1858; 1:95-122, 353-367, 729-735.
[25] Bunge G, Schmiedeberg O. Über die Bildung der Hippursäure. Archiv für experimentelle Pathologie und Pharmakologie 1877; 6:233-245.
[26] Kay JP. Physiological experiments and observations on the cessation of the contractility of the heart and muscles in the asphyxia of warm-blooded animals. The Edinburgh Medical and Surgical Journal 1828; 29:37-66.
[27] Ludwig C, Schmidt A. Das Verhalten der Gase, welche mit dem Blut durch den reizbaren Säugethiermuskel strömen. Berichte über die Verhandlungen der Königlich Sächsischen Gesellschaft der Wissenschaften zu Leipzig, mathematisch-physische Classe 1868; 20:12-72.
[28] Schmidt A. Die Athmung innerhalb des Blutes. Zweite Abhandlung. - Aus dem physiologischen Institute zu Leipzig. Vorgelegt von dem wirkl. Mitgliede C. Ludwig. Berichte über die Verhandlungen der Königlich Sächsischen Gesellschaft der Wissenschaften zu Leipzig. Mathematisch- physische Classe 1867; 19:99-130.
[29] Jacobj C. Apparat zur Durchblutung isolirter überlebender Organe. Archiv für experimentelle Pathologie und Pharmakologie (Naunyn / Schmiedeberg) 1890; 26:388-397.
[30] Clark LC, Jr., Gollan F, Gupta VB. The oxygenation of blood by gas dispersion. Science 1950; 111:85-87.
[31] Kirklin JW, DuShane JW, Patrick RT, Donald DE, Hetzel PS, Harshbarger HG, Wood EH. Intracardiac surgery with the aid of a mechanical pump-oxygenator system (Gibbon type): Report of eight cases. Proceedings of the Staff Meetings of the Mayo Clinic 1955; 30:201-206.
[32] Melrose DG, Aird I. A mechanical heart-lung for use in man. British Medical Journal 1953; 2:57-62.
[33] Aird I, Melrose DG, Cleland WP, Lynn RB. Assisted circulation by pump-oxygenator during operative dilatation of the aortic valve in man. British Medical Journal 1954; 1:1284-1287.
[34] Cross FS, Berne RM, Hirose Y, Jones RD, Kay EB. Evaluation of a rotating disc type reservoir-oxygenator. Proceedings of the Society for Experimental Biology and Medicine 1956; 92:210-214.
[35] von Frey M, Gruber M. Untersuchungen über den Stoffwechsel isolirter Organe. Ein Respirationsapparat für isolirte Organe. Archiv für Anatomie und Physiologie. (Fortsetzung des von Reil, Reil u. Autenrieth, J. F. Meckel, Joh. Müller, Reichert u. Du Bois-Reymond herausgegebenen Archives). Physiologische Abtheilung. Leipzig 1885; 9:519-532.
[36] Bauer W, Dale HH, Poulsson LT, Richards DW. The control of circulation through the liver. Journal of Physiology 1932; 74:343-375.
[37] Bayliss LE, Fee AR, Ogden E. A method of oxygenating blood. The Journal of Physiology 1928; 66:443-448.
[38] Cruickshank EWH. A magnetic blood oxygenator. The Journal of Physiology 1934; 82:26-32.
[39] de Burgh Daly I, Thorpe WV. An isolated mammalian heart preparation capable of performing work for prolonged periods. The Journal of Physiology 1933; 79:199-217.
[40] Hooker DR. The perfusion of the mammalian medulla: the effect of calcium and of potassium on the respiratory and cardiac centers. The American Journal of Physiology 1915; 38:200-208.
[41] Gibbon JH, Jr. Artificial maintenance of circulation during experimental occlusion of pulmonary artery. Archives of Surgery 1937; 34:1105-1131.
[42] Gibbon JH, Jr. The maintenance of life during experimental occlusion of the pulmonary artery followed by survival. Surgery, Gynecology and Obstetrics 1939; 69:602-614.
[43] Gibbon JH, Jr. An oxygenator with a large surface-volume ratio. The Journal of Laboratory and Clinical Medicine 1939; 24:1192-1198.
[44] Bornstein A. Über Durchblutungsversuche an der überlebenden Hundeextremität. Naunyn-Schmiedeberg´s Archiv für experimentelle Pathologie und Pharmakologie 1926; 115:367-374.
[45] Richards AN, Drinker CK. An apparatus for the perfusion of isolated organs. Journal of Pharmacology and Experimental Therapeutics 1915; 7:467-483.
[46] Staub H. Methode zur fortlaufenden Bestimmung des Gaswechsels isoliert durchströmter Organe im geschlossenen System. I. Mitteilung: Über Leberstoffwechsel. Naunyn-Schmiedeberg´s Archiv für experimentelle Patholologie und Pharmakologie 1931; 162:420-451 (420-427 in 1929).
[47] Evans CL, Grande F, Y. HF. Two simple heart-oxygenator circuits for blood-fed hearts. Quarterly Journal of Experimental Physiology 1934; 24:283-287.
[48] Björk VO. Brain perfusions in dogs with artificially oxygenated blood. Acta Chirurgica Scandinavica 1948; 96 (Suppl. 137):1-122.
[49] Zeller O. Versuche zur Wiederbelebung von Tieren mittels arterieller Durchströmung des Herzens und der nervösen Zentralorgane. Deutsche Zeitschrift für Chirurgie 1908; 25:488-559.
[50] Le Gallois JJC. Expériences sur le principe de la vie, notamment sur celui des mouvemens du coeur, et sur le siège de ce principe; Suivies du Rapport fait à la première classe de l´Institut sur celles relatives aux mouvemens du coeur. Paris: D´Hautel, 1812:134-135.
[51] O´Shaughnessy L. Future of cardiac surgery. Lancet 1939; 2:969-971.
[52] Böttcher W, Alexi-Meskhishvili V. Sergej Sergejewitsch Brukhonenko (1890-1960): Pionier des kardiopulmonalen Bypasses in der Sowjetunion. Kardiotechnik 2003; 12:73-77.
[53] Dale HH, Schuster EHJ. A double perfusion-pump. The Journal of Physiology 1928; 64:356-364.
[54] Dixon WE. A simple perfusion apparatus. Journal of Physiology 1922; 56:40-42.
[55] Friedmann E. Zur Technik der Durchströmung überlebender Organe. Biochemische Zeitschrift 1910; 27:87-96.

[56] Kingsbury FB. A perfusion pump. Journal of Biological Chemistry 1916; 28:167-173.
[57] Koehler AE. A simplified apparatus for constant rate injections. Journal of Laboratory and Clinical Medicine 1940; 26:383-385.
[58] von Skramlik E. Ein Apparat zur Durchströmung der Leber. Pflügers Archiv für die gesamte Physiologie des Menschen und der Tiere 1920; 180:1-24.
[59] von Skramlik E. Eine Methode zur künstlichen Durchströmung der Milz. Pflüger´s Archiv für die gesamte Physiologie des Menschen und der Tiere 1922; 194:118-122.
[60] Böttcher W, Merkle F, Weitkemper HH. History of extracorporeal circulation: The invention and modification of blood pumps. J Extra Corpor Technol 2003; 35:184-191.
[61] von Issekutz B. Beiträge zur Wirkung des Insulins. II. Mitteilung: Insulin-Adrenalin-Antagonismus. Biochemische Zeitschrift 1927; 183:283-297.
[62] Fleisch A. Ein automatisch regulierender Durchblutungsapparat mit fortlaufender Registrierung der Durchblutungsgeschwindigkeit. In: Abderhalden E, ed. Handbuch der biologischen Arbeitsmethoden. Vol. Abt. V, Teil 8, Heft 8. Berlin-Wien: Urban & Schwarzenberg, 1935:1007-1026.
[63] Haas G. Die Methodik der Blutauswaschung (Dialysis in vivo). Abderhaldens Handbuch der biologischen Arbeitsmethoden. Vol. 8. Berlin, Wien: Urban & Schwarzenberg, 1935:717-754.
[64] Beck A. Zur Technik der Bluttransfusion. Klinische Wochenschrift 1924; 3:1999-2001.
[65] Beck A. Über Bluttransfusion. Münchner Medizinische Wochenschrift 1925; 72:1232-1236.
[66] DeBakey M. A simple continuous-flow blood transfusion instrument. New Orleans Medical and Surgical Journal 1934; 87:386-389.
[67] DeBakey ME. John Gibbon and the heart-lung machine: a personal encounter and his import for cardiovascular surgery. Ann Thorac Surg 2003; 76:S2188-94.
[68] Saxton GA, Andrews CB. An ideal heart pump with hydrodynamic characteristics analogous to the mammalian heart. Transactions of the American Society for Artificial Internal Organs 1960; 6:288-291.
[69] Böttcher W, Merkle F, Weitkemper HH. History of extracorporeal circulation: The conceptional and developmental period. J Extra Corpor Technol 2003; 35:172-183.
[70] Kolff WJ, Berk HTJ. The artificial kidney: a dialyser with a great area. Acta Medica Scandinavica 1944; 117:121-134.
[71] Kolff WJ, Balzer R. The artificial coil lung. Transactions of the American Society for Artificial Internal Organs 1955; 1:39-42.
[72] Kolff WJ, Effler DB. Disposable membrane oxygenator (heart-lung machine) and its use in experimental and clinical surgery while the heart is arrested with potassium citrate according to Melrose technic. Transactions of the American Society for Artificial Internal Organs 1956; 2:13-17.
[73] Delorme EJ. Experimental cooling of the blood-stream. Lancet 1952; 2:914-915.
[74] Boerema IA, Wildschut WJ, Schmidt JH, Brokhuysen L. Experimental researches into hypothermia as an aid in the surgery of the heart. Arch. Chir. Neerl. 1951; 3:25-34.
[75] Juvenelle AA, Lind J, Wegelius C. A new method of extracorporeal circulation. Deep hypothermia combined with artificial circulation. American Heart Journal 1954; 47:692-736.
[76] Sealy WC, Brown IW, Jr., Young WG, Jr. A report on the use of both extracorporeal circulation and hypothermia for open heart surgery. Annals of Surgery 1958; 147:603-613.
[77] Hooker DR. On the recovery of the heart in electric shock. American Journal of Physiology 1929; 91:305-328.
[78] Ringer S. A further contribution regarding the influence of the different constituents of the blood on the contraction of the heart. Journal of Physiology 1883; 4:29-42.
[79] Lam CR, Gahaghan T, Mota C, Green E. Induced cardiac arrest (cardioplegia) in open heart surgical procedures. Surgery 1958; 43:7-13.
[80] Melrose DG, Dreyer B, Bentall HH, Baker JBE. Elective cardiac arrest. Lancet 1955; 2:21-22.
[81] Gehl H. Hämodynamische Veränderungen bei Anwendung eines künstlichen Herzstillstandes. Langenbecks Archiv für Klinische Chirurgie 1959; 292:678-681.
[82] Cordell AR. Milestones in the development of cardioplegia. Ann Thorac Surg 1995; 60:793-6.
[83] Sealy WC, Young WG, Jr., Brown IW, Jr., Lesage A, Callaway HA, Jr., Harris JS, Merritt DH. Potassium, magnesium and neostigmine for controlled cardioplegia. Studies on the dog using extracorporeal circulation and hypothermia. Archives of Surgery 1958; 77:33-38.
[84] Helmsworth JA, Kaplan S, Clark LC, Jr., McAdams AJ, Mathews EC, Edwards FK. Myocardial injury associated with asystole induced with potassium citrate. Annals of Surgery 1959; 149:200-206.
[85] McFarland JA, Thomas LB, Gilbert JW, Morrow AG. Myocardial necrosis following elective cardiac arrest induced with potassium citrate. Journal of Thoracic and Cardiovascular Surgery 1960; 40:200-208.
[86] Gay WA, Jr. Potassium-induced cardioplegia: evolution and present status. Ann Thorac Surg 1989; 48:441-3.
[87] Gay WA, Jr., Ebert PA. Functional, metabolic, and morphologic effects of potassium-induced cardioplegia. Surgery 1973; 74:284-90.
[88] Tyers GF, Hughes HC, Jr., Todd GJ, Williams DR, Andrews EJ, Prophet GA, Waldhausen JA. Protection from ischemic cardiac arrest by coronary perfusion with cold Ringer's lactate solution. J Thorac Cardiovasc Surg 1974; 67:411-8.
[89] Laks H, Barner HB, Kaiser G. Cold blood cardioplegia. J Thorac Cardiovasc Surg 1979; 77:319-22.
[90] Brodie TG. The perfusion of surviving organs. The Journal of Physiology 1903; 29:266-272.

[91] Bock J. Ein Apparat zu Infusionsversuchen. Archiv für experimentelle Pathologie und Pharmakologie 1907; 57:177-182.
[92] Skutul K. Über Durchströmungsapparate. Archiv für die gesammte Physiologie des Menschen und der Thiere 1908; 123:249-273.
[93] von Euler US, Heymans C. An oxygenator for perfusion experiments. Journal of Physiology 1932; 74:(Proc.) 2P-3P.
[94] Carrel A, Lindbergh CA. The Culture of Organs. New York: Paul B. Hoeber (Hamish Hamilton Med. Books. London), 1938.
[95] Gibbon M. Personal recollections of the earliest years of the development of the heart-lung machine. Journal of Extra-Corporeal Technology 1978; 10:77-88.
[96] Schwiegk H. Wiederbelebung durch einen künstlichen Kreislauf. Klinische Wochenschrift 1946; 24/25:104-111.
[97] Jongbloed J. The mechanical heart lung system. Surgery Gynecology & Obstetrics 1949; 89:684-691.
[98] Dennis C. Perspective in review. One group's struggle with development of a pump-oxygenator. Trans Am Soc Artif Intern Organs 1985; 31:1-11.