History of Extracorporeal Circulation: The Conceptional and Developmental Period

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Abstract: The development of modern techniques in extracorporeal circulation is the result of the combined efforts of physiologists, physicians, and engineers. Early experimental work at the end of the 19th century was accomplished by physiologists, such as von Schröder, von Frey, and Gruber, as well as Jacoby. These scientists laid the foundation for three different artificial oxygenation devices for experimental isolated animal organ perfusion. The developed bubble, film, and isolated lung oxygenation methods developed were later used for the first clinical cardiopulmonary bypass procedures in humans. For continuous perfusion experiments, closed circulation circuits were put into use. In a second step, during the first half of the 20th century, scientists and physicians, such as Brukhonenko, Gibbon, Crafoord, Björk, and Jongbloed were working on the refinement of these methods for intended application during cardiovascular operations in humans. Refined bubble and film oxygenators together with the modern blood pumps in closed circulatory systems were assembled as pump oxygenators, later called heart–lung machines. They were used in the first clinical cases of extracorporeal circulation for heart surgery in the second half of the 20th century by Dennis, Dogliotti and Constantini, and Gibbon. Keywords: history, bubble oxygenator, film oxygenator, extracorporeal circulation, heart-lung machine. JECT. 2003;35:172–183

IDEA AND FIRST STEPS

The beginning of the historical development of extracorporeal circulation is usually associated with César Julien Jean Le Gallois (1770–1814). He stated in 1812 in his monography “Expériences sur le principe de la vie,” which was translated into English by N. C. and J. G. Nancréde and published one year later in America: “But if the place of the heart could be supplied by injection—and if, for the regular continuance of this injection, there could be furnished a quantity of arterial blood, whether natural, or artificially formed, supposing such a formation possible—then life might be indefinitely maintained in any portion; and consequently, after decapitation, even in the head itself, without destroying any functions peculiar to the brain. Not only life might thus be kept up both in the head and in any other portion separated from the body of an animal, but might also be re-produced after its entire extinction. It might be restored likewise to the whole body, and thereby a complete resurrection be performed in the full extent of the word” (1,2). Le Gallois did not perform perfusion experiments himself. The illustration in his publication depicts a decapitated rabbit kept alive by pulmonary inflation performed with a small syringe, and not, as often falsely stated, artificial perfusion through the carotid arteries.

James Phillips Kay from Edinburgh reported practical perfusion experiments in 1828. During his experiments, he withdrew arterial blood from the carotid arteries and observed muscular contractions of the lower extremities after injection of this blood into the abdominal aorta of a rabbit. He showed that “arterial blood is more favourable to contraction than venous” and, after further experiments, that “dark blood is therefore less favorable than arterial to the contractility of muscle, but its presence in the tissue supports this power a considerably longer period than when the artery is simply tied” (3).

Eduard Brown-Séquard in 1858 injected blood into the arms of decapitated criminals with a syringe and showed a reaction on stimulation of these perfused extremities; whereas, in nonperfused extremities, no such reaction could be provoked (4). He undertook early attempts in artificial oxygenation of blood by shaking black blood and, thereby, transforming it into red blood. After injections of
FIRST PERFUSION EXPERIMENTS

The first described continuous organ perfusions were probably carried out by Carl Eduard Loebell from Marburg, Germany, during kidney perfusions while researching urine secretion. He mentioned these procedures in his Dissertation Inauguralis “De conditionibus, quibus secretiones in glandulis perficiuntur” of 1849 (5). To compare the volume of secreted urine to the kidney perfusion blood volume and ureter pressure, Loebell perfused isolated pig kidneys with defibrinated and incoagulable blood and observed that the bright red arterial blood extravasated in dark color and with higher viscosity from the renal veins; whereas, a clear fluid came out of the ureter (see Figure 1).

To continue the experiments of Loebell, Ernst Bidder of Dorpat, Russia (now in Estonia), in 1862 constructed a primitive perfusion apparatus (6). Pressure on the blood in the apparatus could be created with a glass cylinder filled with mercury, which ended in a glass basin filled with blood. The level of mercury in the glass cylinder could be varied at will, and the blood pressure in the renal artery could be altered with this technique. The blood was collected from the artery of a living animal, defibrinated by stirring with a rod, and filtered through fine linen to remove the remaining clots (see Figure 2).

Alexander Schmidt at the Physiological Institute at Leipzig on advice from his professor, Carl Friedrich Wilhelm Ludwig, carried out experiments on oxygenation of venous blood by adding oxygen. He also developed methods for estimating oxygen and carbon dioxide content in...
venous and arterial blood. Schmidt established artificial perfusion as a method and perfused kidneys of dogs with defibrinated, oxygenated, and linen-filtered blood. The apparatus he developed allowed regulation of blood pressure in a way similar to that of Bidder. Alexander Schmidt reported on his experiments on 9 November, 1867, (7) (see Figure 3). One year later, Ludwig and Schmidt performed perfusion experiments with muscle tissue of dogs. Defibrinated blood was arterialized by agitation in atmospheric air. They stated: “Undoubtedly an artificial stream of arterial blood conserves the viability of muscles and nerves and also restores it in these structures when excitability has been exhausted” (8) (see Figure 4).

In 1876, Bunge and Schmiedeberg, at the Laboratory for Experimental Pharmacology in Strassburg, agitated dark venous blood in atmospheric air, as in the experiments of Ludwig and Schmidt, until it assumed the bright red, arterial color (9). At that time, pump devices were not yet known for this kind of experiments, so the adjustable water pipe pressure was used as driving force for blood perfusion. The blood reservoir was inserted into a warm water bath for the first time, so that the perfusion experiments were no longer carried out at room temperature.

In 1882, actually in search of the location where blood urea nitrogen was produced, Waldemar von Schröder in Strassburg attempted artificial perfusion of isolated organs. During his experiments, blood was arterialized with an apparatus he constructed. He oxygenated the blood by bringing an air current into contact with the blood. Thus, his experimental work represents the first form of bubble oxygenation, although the inherent problems were already evident: “Because of the rapid air current passing through the blood, foaming often occurs quite heavily” (10). In the following year, M. Abeles at the Ludwig Laboratory made use of an apparatus developed by von Schröder and used pure oxygen for the first time instead of air (11). Other researchers also adopted this method of oxygenation in the following period (12,13).

![Figure 3. Experimental setup of Schmidt (1867): A reservoir filled with mercury (1) is mounted on a pole, adjustable in height. It is connected with a rubber tubing to the blood reservoir (2). The pressurized blood flows through a stopcock (3) into the artery and exits from the vein of the isolated organ, kept in a glass capsule (4).](image)

![Figure 4. Wood engraving of the experimental setup of von Ludwig and Schmidt (1868). The blood stream from the reservoir (F) to the tissue on the glass plate (T) is regulated by the relative height of a reservoir containing mercury (Q) on a variable stack of thin boards (r).](image)
CLOSED CIRCULATORY SYSTEMS

A great advance in the method of perfusion was the construction of the first closed artificial circulation system by Max von Frey and Max Gruber from the Physiological Institute at Leipzig. Until their invention was introduced in 1885, the perfusion procedure had to be interrupted to oxygenate the blood flowing out of the vein of the organ and for subsequent transfer into the arterial reservoir. Closed circulation systems need a pumping mechanism, as gravity alone is not sufficient (14), nor is varying the height of the container with the perfusate (15) or pressurizing the blood volume in the container, as the circulating blood volume has to be returned to the reservoir. Subsequently, closed circulatory systems were also constructed by Jacobj [1890 (16); 1895 (17); and 1923 (18); Brodie (1903) (19); Embley and Martin (1905) (20); Mandel (1908) (21); Friedmann (1910) (22); Neubauer and Groß (1910) (23); Hooker (1910) (24); Richards and Drinker (1915) (25); von Skramlik (1920) (13,26); Dixon (1922) (27); and Bauer, Dale, Poulsson, and Richards (1932) (28) and used for experimental organ perfusion. The construction by von Frey and Gruber in principle shows marked similarities to the assembly of later heart–lung machines. It consisted of a double-acting pump in the form of an injection syringe with a capacity of 10 mL, which imitated the heart action, and two valves. This pumping system produced a pulsatile flow. Because of this pulsatile driving force, “as a result of the swinging movement of the blood elements and through the constant change of the vessel diameter, obstructions occurred less frequently and resolved quicker, as sedimentation and adhesions of the cells happened to a lesser extent” (29).

An important component of this artificial circulation was the addition of the facility “which was able to replace the lung.” Von Frey and Gruber developed the first film oxygenator for this purpose. Blood in the form of a thin film was oxygenated inside a slowly rotating cylinder by an oxygen atmosphere. The temperature of the arterial blood was regulated by a “preheater.” As with current heart–lung machines, the circulation incorporated several pressure and temperature measuring devices as well as sample ports. By insertion of glass cannulae into both the aorta and vena cava, artificial perfusion of a dog’s rear part was performed (30). Following electrical muscle stimulation during this experiment, measurements of “the consumption of oxygen caused by its use by the tissue and the absorbed carbon dioxide” were performed, as stated in their reports dated 20 November, 1883, (see Figure 5).

Carl Jacobj considered this apparatus, as constructed by von Frey and Gruber, too expensive and its use too complicated. He constructed a new perfusion apparatus at Strassburg, which he called a “hematisator.” Artificial gas exchange was described similar to the technique of von Schröder: “Caused by the close contact of both blood and air, the former has the opportunity to continuously deliver its carbon dioxide and to take up new oxygen from the air. . . . The blood was used undiluted and had always a nice, bright red color in the arterial tubings, while it exited in a dark and bluish-red color from the vein . . . .” Thus, for the first time, the principle of a bubble oxygenator was incorporated into a closed perfusion system. He pointed out, “that the more the method of artificial perfusion is perfected and the better we succeed in supplying the isolated organ with blood under the same conditions as in the living body, the more symptoms of life are preserved in a normal way and are accessible to examination.” This apparatus, on the one hand, was to be suitable for quantitative analysis of the blood and blood gases, and “on the other hand permits the production of circulation conditions similar to natural conditions, and is easy to perform and to handle” (16). With the help of this apparatus, an uninterrupted blood stream could be led through an isolated pig kidney. As with von Frey and Gruber’s system, great importance was attached to pulsatile flow character, because it “is of utmost importance for blood flow velocity in the organ and also for its nourishment” (see Figures 6 and 7).

In 1889, Hamel in Bern, Switzerland, was also able to prove the value of pulsatile perfusion in an experiment (31), and several researchers subsequently underlined his results (24,32–34). His “electrical pendular cock” was able to produce an intermittent perfusion pressure in the preparation (see Figure 8). Jacobj’s pump consisted of a rubber balloon that was compressed rhythmically between two boards. This pump form was later adopted by Embley and Martin (20) and Neubauer and Groß (23).

To realize arterIALIZATION of the blood in “a way which resembles the natural way, so that damage of the blood, caused by direct contact with air, is excluded as much as possible,” Jacobj in 1895 modified his machine. The gas exchange of his “hematisator” was accomplished through an artificially respirated natural lung (17). Now, two organs had to be perfused simultaneously: the lung for the purpose of oxygenation as well as the organ to be examined. Because of the use of an isolated lung as an oxygenator, the harmful direct blood-gas-contact could be avoided by a physiologic membrane. This method for gas exchange was later taken up by Embley and Martin (1905) (20); Dale and Schuster (1928) (35) as well as Daly and Thorpe (1933) (36).

Whereas previously, almost all perfusion experiments were accomplished with the help of defibrinated blood, Jacobj, for the first time, inhibited coagulation pharmacologically. For anticoagulation, he used an extract of 10 to 20 leeches following the specifications of Haycraft, which he called “hirudin.”
PROGRESS AND NEW FIELDS OF APPLICATION

In 1903, T. G. Brodie (London) attempted the construction of an apparatus that would approximate the ideal equipment for organ perfusion (19). He developed a reciprocating pump and accomplished “aeration” by mixing defibrinated blood and air in the pump chamber. However, he also described the difficulties that developed because of foaming in the pump: “If too much air is admitted a great deal of frothing occurs in most cases, and this entails a serious loss of blood.” Earlier experiments led him to the conclusion that utilization of blood of the same species would be much better, preferably only blood of the same animal. First and important thoughts on minimizing the priming volume were voiced: “With care in economising the tubing leading to and from the organ it is quite possible to perfuse most of the organs of the cat using the animals own blood only.” However, he also showed the limits of hemodilution: “In most organs and tissues, however, and notably in the lungs, dilution of the blood with saline leads to the production of considerable oedema.” Brodie’s apparatus was frequently used and modified by other physiologists (37,22,38).

During the course of experiments for resuscitation by way of arterial perfusion, O. Zeller from Berlin found out that a lack of blood cells, resulting in a lack of oxygen, kills central nervous organs (39). In 1908, Zeller communicated his vision that artificial perfusion of humans could save lives in an emergency and could support lives during cardiovascular operations: “I would imagine the course of events like this: During cardiac massage and artificial respiration the apparatus is filled with Locke’s solution, containing hirudin and blood gained by venesection, perfused...
with oxygen; quickly expose an Art. brachialis and arm with a cannula. The other upper extremity is tied and the Aorta abdominalis compressed, to reduce the perfused area; a vein is prepared for venesection. Precious time will have passed. This can therefore only be a matter of a last attempt. Rather, action would be imaginable during operations, where one has to anticipate exsanguination and cardiac arrest, where one is able to prepare for such an event in advance, for example during suturing of heart wounds or during the considered removal of emboli from the lung arteries by von Trendelenburg. Whether of course the escaping life can be salvaged, may be shown in the future” (39).

One of the first electrically powered syringe pumps was developed in 1907 by Johannes Bock at the Pharmacological Institute at the University of Copenhagen (40). His apparatus for infusion experiments consisted of a double syringe and functioned, according to his statement, with high precision and needed no surveillance. Successive modifications of such syringe pumps were described (22,41). In 1913, Fröhlich, in Vienna, first described the application of an electrically powered rotary pump for permanent perfusion of organs (42).

An apparatus for maintenance of perfusion of isolated mammalian organs with defibrinated or anticoagulated blood with hirudin was constructed by Richards and Drinker (University of Pennsylvania) in 1915 (25). They stated: “While we agree with Starling in his dictum that it is
impossible to construct an aerating apparatus for blood which shall approximate to the efficiency of the lungs we have made a device which has answered the purpose which the experiments thus far have involved, i.e., the adequate continuous oxygenation of the blood necessary to supply such an organ as the dogs kidney. Richards and Drinker chose glass as pump material, because use of metal or other material in contact with blood was expected to create complications. Oxygenation of the blood was achieved by pumping it into the straight end of a glass tube where it squirted out of small holes and was caught in the meshes of heavy, loosely woven cloth, surrounded by an oxygen atmosphere. The cloth first used was later substituted by heavy silk pongee. The problem of particulate embolizations was evident with this setup because of infarctions of perfused kidneys, caused by textile fibers. A first clot-trapping device was developed by Langendorff in 1897 in the form of interwoven horsehair (43); later, loosely packed glass wool was usually used for that purpose. Air traps were in use in the form of a T-junction, incorporated into horizontal tubing. As early as 1910, Rohde pointed out that bubbles formed in the perfusate by release of oxygen when a solution saturated at a low temperature was rewarmed at a different site of the perfusion apparatus. He developed his own air trap (44). Other bubble traps were developed by Friedmann (1910) (22) as well as by Neubauer and Groß (1910) (23).

In 1919, Hooker demonstrated with his concept for the "aeration" of blood: "as the blood falls upon a rotating disc it is thrown against the side of an inverted bell-jar and runs down in a thin film exposed to the contained air and collects in a suitable reservoir below" (24,45). Other investigators also led blood as film across rotating discs, plates or spirals (36,46–50).

Another attempt to lead blood for oxygenation as a film across a large surface was reported by A. Bornstein of Hamburg in 1926 (51). The blood in his apparatus flowed through a vessel filled with glass beads, into which a continuous flow of oxygen sparkled through a water bottle. Further methods of film oxygenation were demonstrated by Staub in 1931, with his screen oxygenator, where parallel glass plates covered with cloth where suspended in an Ebonit frame with blood flowing down their sides (52), and in 1939, Gregory presented his oxygenation system, which consisted of four parallel oxygenators, where blood was directed onto the inner surface of cylinders from above (53).

In 1932, von Euler and Heymans reported on their oxygenator, in which blood was sprayed into a glass balloon of a volume of 5–10 L simultaneously with an oxygen–carbon dioxide mixture to prevent acapnia (54). This method was, however, associated with a high hemolysis rate, according to later investigations by Björk (55).

**PREPARATION FOR CLINICAL USE**

Charles A. Lindbergh, having become famous after his solo flight across the Atlantic on 20 and 21 May, 1927, did some research on options to bypass the heart, triggered by the mitral valve disease of his wife’s sister. To prove that isolated organs were able to live on when perfused with nutritive solution, Lindbergh and Alexis Carrel at the New York Rockefeller Institute developed a system for oxygenation of the perfusate (56,57). In publications of the year 1935, Carrel and Lindbergh described their model, which enabled an organ to live outside the body, “thereby for the first time realizing the concept of Le Gallois.” This apparatus maintained a sterile pulsating circulation with a medium of blood serum and growth-stimulating solutions. With this system, consisting of several glass chambers and powered by pulsating gas, hearts, ovaries, and kidneys could be perfused.

After Sergei Sergeevich Brukhonenko (also: Brychonenko) from Russia had seen serious injuries of hearts and great blood vessels during the First World War, he considered possibilities to support blood circulation during operations on these injuries. He reported experiments with artificial circulation in 1927 at the National Chemo-Pharmaceutical Research Institute at Moscow on isolated heads and for the first time on the whole body, when heart and lungs were excluded temporarily, in connection with the “peculiar quality of the Bayer preparation ‘Germanin (B.205)’ to prevent coagulation” (58). In conjunction with S. Tchetchuline, he had been developing the “autojector” since 1926; this was an apparatus for artificial circulation with blood of warm-blooded animals. It consisted of two...
mechanical diaphragm pumps with a valve system and rhythmically ventilated lungs of an animal, which served as oxygenator, where one pump moved the venous blood through the lungs, and the second pump maintained systemic perfusion. On 1 November, 1926, the circulation of an animal whose heart was stopped was maintained for 2 hours with such an apparatus. After the description of eight further experimental perfusions, Brukhonenko wrote that thus, as a matter of principle, the possibility of replacement of the heart function with a temporarily stopped native heart had been demonstrated, even if the corresponding technology had to be refined. On 1 June, 1928, similar experiments were demonstrated on the occasion of the 3rd Physiology Congress of the Soviet Union (59), and on 11 October, 1928, he wrote: “Would not this method, duly perfected, be useful in clinical medicine; notably in those cases where it would be essential to replace, if only for a time, the work of the failing human heart? Without going more deeply into this question we can state as a result of the present work that in principle artificial circulation is applicable to man not only clinically, but perhaps also for certain operations on the temporarily arrested heart. For its achievement, however, a suitable technique would have to be worked out....The solution of the problem of the artificial circulation of the whole animal opens the door to the problem of operations on the heart, for example on the valves” (59).

Brukhonenko had his machine patented on 29 November, 1928, in the Soviet Union and in the following year also in Germany. From 1931 onward, he combined his perfusion experiments with deep hypothermia by cooling dogs to 3°C. With the help of this apparatus, Terebinski operated for the first time on the valves of the open heart in animal experiments in 1926 and conducted hundreds of such operations between then and 1937 (60). The donor lung of the device was replaced in 1936 by a bubble oxygenator developed by Brukhonenko, which he registered on 31 March, 1937, (61–65). The experiments for isolated perfusion of a dog’s head were introduced in a French newspaper (66), and in a Berlin newspaper of 17 March, 1929, George Bernhard Shaw was cited in a private letter to a Berlin woman: “I straightforwardly feel the temptation to have my head cut off myself to be able to go on dictating plays and books without being disturbed by illnesses, without having to dress and undress, without having to eat, without having anything else to do than to produce masterpieces of the dramatic art and of literature. . . . A university where all chairs were occupied by a number of the finest brains of the country, with nothing else than a doll attached—where, in short, all the lecturing would be purely cerebral, would be enormous progress compared to the present state” (translated from German) (67) (Figure 9).

Triggered by the death on 3 October, 1930, of a patient who died following pulmonary embolism, John Heysham Gibbon in Philadelphia began constructing machines that aimed to be capable of maintaining heart and lung function for the short time during correction of a circulatory defect. In 1937, Gibbon described his first experiments with cats, whose heart and lung function he was able to replace artificially for 25 minutes during occlusion of the pulmonary artery (68). For anticoagulation, he used heparin that had been discovered by Jay McLean in 1916 (69). However, it was not until 1931 that heparin was made available in purified form and sufficient quantities (70). Venous blood was fed from above onto the inner wall of a vertical, rotating, and cylindrical film oxygenator. A thin blood film formed that was oxygenated by an atmosphere of 95% O₂ and 5% CO₂. The blood collecting underneath in a reservoir was first pumped back into the artery by pulsatile pumps after Dale and Schuster (35), which were then modified by de Burgh and Daly (71). According to the latter’s reports 2 years later, he had improved the oxygenation system (72), and the pulsatile membrane pumps had been replaced by the roller pump (73), modified by DeBakey (74). Although the roller pump was patented as early as 1855 (75) and subsequently used for numerous blood transfusions (76–80), it was put into use in the course of organ perfusion as late as 1927 by Issekutz (81), however, first for transportation of the oxygen needed for oxygenation and then as a blood pump by Fleisch in 1935 (82).

In contrast to Gibbon, who from the start was striving for perfusion of the whole body, other pioneers in the field of cardiopulmonary bypass tried to restrict the area to be perfused because of the limited capacities of their equipment. Because other organs and tissues were able to tolerate an interruption of the circulation for a longer period of time, the limiting factor for the success of an open-heart operation was ischemia of the brain with resulting death or at least remaining neurologic damage.

In 1939, Laurence O’Shaughnessy (London) reported on his experiments that had been going on for the 3 previous years. He had perfused the brains of dogs and cats with Ringer’s solution and the addition of hemoglobin, amounting to 5% of the total volume, as blood replacement, to maintain cerebral circulation artificially during heart operations (83). He calculated oxygen content of 18.5 mL/100 mL for blood and a smaller oxygen content of 5 mL/100 mL for his replacement solution. He tried to compensate for this condition by a higher perfusion flow. Experiments of this kind were survived by several dogs and cats. O’Shaugnessy ended his report on the future of cardiac surgery with these words: “This method of cerebral perfusion is clearly unfitted for immediate clinical application, but it is presented as an example of the sort of work necessary for the further advance of the surgery of the heart.”

As Clarence Crafoord in Stockholm had shown since...
1935 with his experiments and the first clinical correction of coarctation of the aorta in 1944, other organs were able to withstand a period of up to 25 minutes without perfusion. Because of the far lower tolerance for ischemia of the brain only, this organ was to be supplied with an appropriate perfusion flow by a heart–lung machine (84). During a visit to John Gibbon in Philadelphia in 1939, Crafoord had been able to watch experimental extracorporeal circulation and learned that gas exchange was possible with a thin blood film on a large surface in oxygen atmosphere (85, 86). Together with his engineer, Emil Andersson, Crafoord had an “artificial heart–lung machine” constructed in 1946. Viking Olov Björk, one of his assistants in 1948, reported on an oxygenator in which venous blood was led onto the bottom of a horizontal cylinder, in which vertical discs, mounted on a central axis, were rotated and, thereby, dipped into the blood (55, 87). An electric motor moved the axis, distributing the blood on the surface of the discs. With 40 discs, a surface comparable to that of the early Gibbon machine could be achieved. With this apparatus, the brains of dogs were perfused in isolation for up to 30 minutes.

Like Gibbon, the physiologist J. Jongbloed in the Netherlands, aimed to perfuse the whole body, because he wanted to protect viable organs, other than the brain, which would suffer from longer circulatory arrest (88). In comparison to the Crafoord oxygenator, which was designed to perfuse the brain exclusively, the Jongbloed oxygenator had to oxygenate an approximately five times larger blood volume in the same time for systemic perfusion. He used modified pumps after Dale and Schuster and constructed a spiral oxygenator, where gas exchange took place at a thin blood film on the inside of several synthetic tubings. Six synthetic tubings with a length of 10-m each and an internal diameter of 18 mm were arranged in a spiral and rotated slowly around their central axis. Gas exchange for up to 4.2 L of blood per minute was possible. This oxygenation system was, therefore, able to oxygenate an extracorporeal blood flow resembling the basic cardiac output of humans. Jongbloed reported on dogs that were perfused for 2 hours with his apparatus and were still living 1 year later.

The earlier method of bubble oxygenation, which had to be abandoned because of the unsolved problems associ-
ated with foaming, was reexamined in 1950. Leland Clark, Jr. and Frank Gollan, as well as Vishwa B. Gupta improved and developed methods for defoaming with methylpolysiloxane (89). For the purpose of organ perfusion, Clark had first constructed membrane oxygenators with cellophane membranes, whose capacity with respect to oxygen transfer was, however, limited. Using the bubble method, quick oxygenation was achieved, but foaming initially led to uncontrollable problems. After attempts to reduce the formation of foam with alcohol, Clark’s experimental animals slept for several days because of alcohol intoxication. During another experiment, he accidentally discovered that the silicone lubricant of a stop-cock instantly reduced foaming, and thereafter, he used silicone for defoaming during bubble oxygenation (90). Only after introduction of this method for defoaming of the blood could bubble oxygenation be used routinely, preparing the ground for widespread clinical application in the time to follow.

**FIRST CLINICAL APPLICATIONS**

The heart–lung machine developed by Clarence Dennis was put into clinical use for the first reported case on 5 April, 1951. A 6-year-old girl was scheduled for correction of a large interatrial defect in Minneapolis. An attempt at repair had been deferred in anticipation of the availability of the heart–lung machine. During the operation and while the patient was on cardiopulmonary bypass, excessive blood loss occurred and subsequent massive transfusion of citrated blood was necessary. “Late in the repair it was appreciated that the force of the heart beats was extremely weak, and no vigorous beats occurred after removal of the cannulas. Belatedly, this was recognized as a citrate effect...”. The authors concluded despite of the unsuccessful outcome: “This apparatus has behaved admirably in one human trial... This apparatus appears to have a place in further development of the surgery of cardiac abnormalities” (91). In the following year, the first successful clinical open-heart procedure took place at the same hospital on 2 September, 1952. Floyd John Lewis closed an atrial septal defect in a 5-year-old girl with the aid of hypothermia and inflow stasis (92).

The first clinical use of extracorporeal circulation in the form of partial cardiopulmonary bypass was successfully performed by Mario Dogliotti and A. Constantini in Turin, Italy. On 9 August, 1951, the condition of a 49-year-old male patient deteriorated during surgical exposition of a mediastinal tumor. The patient became cyanotic, and blood pressure was unobtainable. Extracorporeal circulation was instituted with a previously prepared apparatus, and “after a few minutes of artificial circulation at the rate of about one liter per minute the patient’s condition improved considerably. It was possible then to continue with the surgical procedure; the tumor was completely removed and the patient made an uneventful convalescence” (93,94)

The conceptional and developmental period terminates with the first reported case of successful intracardiac repair using total cardiopulmonary bypass: John Heysham Gibbon in Philadelphia, closed a large atrial septal defect in an 18-year-old female patient on 6 May, 1953 (95).

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