... “During the hours that night, John watched the patient’s distended veins and recorded the faultering pulse, respirations and blood pressure, the thought occurred to him and constantly recurred to him that her conditions could surely be improved if only there were some form of continuously withdrawing some of the blue blood from the swollen veins into an apparatus where the blood could pick up oxygen and discharge carbon dioxide, and then be pumped back into the patient’s arteries” [1].

Mary H Gibbon, “Recollections”
History contains several examples of monumental successes constructed on foundations planted by numerous trials and errors. In sciences, it is exceptional for a single individual to make a great discovery. In most cases, science walks one step at a time, and each researcher depends on the work of his predecessors. We can, therefore, establish that the history of cardiopulmonary bypass emanates from a distant past, confounded with the description of blood circulation by William Harvey in his memorial publication from 1628 entitled “De Motu Cordis”. In this work Harvey establishes, in reality, not only the first description of blood circulation in the human organism starting from the heart, but also the general principles of physiology, by the description of a methodology to study natural sciences [2]. Because of this extraordinary contribution from the beginning of the 17th century, Harvey is considered the father of Cardiology.

The descriptions of Harvey were difficult to accept by many researchers, mainly because capillary anatomy was only described and demonstrated in 1661 by Malpighi, thereby completing the existing knowledge about blood circulation [3]. From 1660, physiologists of Oxford, including Boyle, Hooke and Lower, described some experiments which were fundamental to the understanding of respiratory physiology. Up to that time, exchange of substances between the blood and the air was only a speculative notion. At the beginning of the 19th century, 175 years after the description of circulation, Lavoisier developed his studies on respiration, concluding that it was analogous to combustion with the end products being carbon dioxide and water [4].

During most of the 19th century, the interest of physiologists in relation to circulation was focused on the study of organs isolated from the organism. Many of those works were essential to establish the foundations of cardiopulmonary bypass.

Cardiopulmonary bypass, as a support technique in heart surgery is, from a historical
point of view, relatively recent. The date of 6th May, 1953 represents an important mark in this technology. On that day, an 18 year-old girl - Cecilia Bavolek - suffering from an interatrial communication, entered the history as the first successfully patient operated with the utilization of an artificial heart-lung machine to allow access to the interior of the heart (Fig. 1.1). John Gibbon and his wife Mary Gibbon, after a long period of research and experimentation, created an artificial respiratory and circulatory system, capable of temporarily supplying all the metabolic requirements of a human being [5-9].

Historical reports cite the young lady as being Cecilia Bavolek, an 18 year-old at the time of operation. However, documents from the Jefferson hospital, where the operation was performed, showed the following information:

1. The patient, a client of Dr Donald B. Lewis, was referred to Jefferson hospital with the following transfer letter:

   To the Jefferson hospital: Please hospitalize Miss Celia Bivalek in the department of Dr John Gibbon for heart surgery. At the moment the patient presents with well compensated mitral stenosis.

   Authorization for the surgery was signed by the mother and the sister of the patient, Mary Bavolek and Josephine Bavolek, respectively. Considering that the surnames of mother and sister of the patient were the same, Bavolek, it is improbable that the patient, in truth, was called Bivalek, as Dr Lewis had written on the referral letter for hospitalization. And, as the name is not common among Americans, it is also highly probable that, with the emotion of referring an 18-year-old for a surgery that had never previously been performed successfully, Dr Lewis had written Celia instead of Cecilia. The patient was, thus, referred for surgery with the diagnosis of compensated mitral stenosis. A pre-operative review of the case in the department of Dr Gibbon, correctly diagnosed an interatrial communication. History or more specifically, the repetition of historical data may, sometimes, distort details and modify the meaning of facts. Cardiac surgical history registers that Cecilia Bavolek was submitted to correction of an interatrial communication with cardiopulmonary bypass performed by John and Mary Gibbon in May 1953. Documents, although important, do not always register the facts exactly in the form they occur, prejudicing history but in this case benefiting the Bavolek family [10].

   By operating that machine Mary Gibbon, became the first perfusionist in history, while J. Gibbon performed the first successful intracardiac surgical correction. In her autobiography, Mary Gibbon describes how the idea which led to the development of cardiopulmonary circulation appeared [1-3].

   Some unsuccessful attempts using artificial heart-lung systems were made before Gib-
Dogliotti and Constantini [11] in Italy in 1951 published a case where cardiopulmonary circulation was used in humans as circulatory support to remove a mediastinal tumor. In the same year, Dennis et al. [12,13], in the University of Minnesota, operated on two children using extracorporeal circulation and an oxygenator based on discs from an idea previously developed by Craaford. The first, a six year-old, died due to the complexity of the heart disease at that time. Instead of a simple interatrial communication, as was expected, the infant had a partial form of an atrioventricular septal defect. The second child, suffering from a simple interatrial communication, died from the consequences of air embolism, due to a leak in the arterial reservoir of the oxygenator. Another patient reported by Helmsworth [14] in 1952, died as a consequence of insurmountable difficulties with the surgical procedure.

THE CONTRIBUTION OF PHYSIOLOGISTS

Some ideas about perfusion had already been discussed in several papers by some physiologists since the 19th century.

Le Gallois, in 1813, formulated the first concept of artificial circulation. He postulated that “if it were possible to replace a heart by some artificial manner to pump the blood, it would not be difficult to keep alive, for an undetermined period of time, any part of the organism”. Le Gallois worked with decapitated rabbits and injected blood through their carotid arteries. However, he was unable to prove his theory, mainly, because he used unoxygenated blood [15]. According to some recent studies [125] 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 stated, artificial perfusion through the carotid arteries. In 1828, Kay demonstrated that an ischemic muscle can recover its contraction while being perfused with blood [16].

Stenton, Bichat and others observed that the cerebral and neuromuscular functions could be temporally restored after apparent death if the brain was perfused with blood [17].

Brown-Sequard, between 1848 and 1858, obtained oxygenated blood by shaking the blood in air and demonstrated the necessity of blood as a perfusate to obtain neurological activity in severed heads of mammals. He perfused the organs using syringes. Experimenting with organs from executed criminals, he used his own blood to demonstrate that the muscles, at the stage of rigor mortis and without response to galvanic stimulation, could be reactivated by perfusing of oxygenated blood while the non-perfused part of the body perished [4,16,17].

In 1849, Lobell studied artificial perfusion of the kidneys, attempting to obtain some
function in resected organs [18].

Ludwig and Schmidt, in 1868, developed an apparatus to infuse blood under pressure in an attempt to perfuse isolated organs [3,4,18].

Von Schroeder constructed the first, though extremely rudimentary, bubble oxygenator in 1882, in which the air was bubbled into a reservoir containing venous blood [19].

Von Frey & Gruber, in 1885 constructed the first artificial heart-lung system in which oxygenation of the perfusate could be achieved without interrupting blood flow. This system, however, was developed for isolated organ perfusion. The oxygenating section of the apparatus consisted of a 70cm-long glass cylinder which revolved around its longest axis. Blood was poured in the inner surface of the cylinder and spread out as a thin film in contact with air. The oxygenated blood was pumped by means of a syringe [16,17].

Hamel constructed a pendulum that periodically interrupted the flow of perfusate to produce a pulsatile flow [19].

Physiologists rapidly understood the importance of pulsatile perfusion to obtain better preservation and functioning of isolated organs. In 1903, Brodie constructed another apparatus in which perfusion of organs used the blood of an animal. A pulse was obtained using a flexible rubber tube that was compressed using a wooden arm on the arterial line [20].

In 1895, Jakobj established a method of isolated organ perfusion which used gas exchange through the lobes of animal lungs [21].

During initial experiments of organ perfusion, procedures were complicated due to blood coagulation. Researchers, as a rule of thumb, had to use “defibrinated” blood for their experimental works.

With the discovery of the ABO blood groups by Landsteiner in 1900, new possibilities appeared for experimental work with researchers preventing some of the problems that, until then, were encountered with the use of blood from animal donors [22].

In 1916, Howell and Mc Lean [23,24], while the latter was still a medical student, discovered heparin, studying extracts from animal livers, providing a decisive breakthrough to researchers who worked with blood, both “in vivo” and “in vitro”, specifically for organ perfusion which, with the inhibition of coagulation, became more successful.

Brukhonenko, in Russia, in 1926, developed a system which incorporated a pump to propel venous blood through a donor lung, with a second pump maintaining the circulation of the head or body of an experimental animal. This researcher postulated that “the transition between natural and artificial circulation does not necessarily implicate the death of an experimental animal, that is, life can continue under the conditions imposed by an artificial circulation” [25].
THE WORK OF JOHN AND MARY GIBBON

In her “Recollections”, cited by Litwak [3] in 1971, Mary Gibbon reported in detail how the idea to develop an artificial heart-lung machine started:

“In January 1930, John finished his fellowship in Philadelphia and came to Boston for one year of surgical research with Dr. Churchill. We met in Boston when he started to work. I was the laboratory technician of Dr Churchill at that time. We worked together during one year and married in 1931.

In February of that year, a patient from Massachusetts General Hospital who was suffering from severe postoperative pulmonary embolism was taken to the operating room. John was placed in charge of checking the patient’s vital signs at 15-minute intervals for the entire night, while Dr Churchill and his team waited to decide about the operation. During the hours of that night, John observed the distended veins of the patient, his weak pulse, respiration and pressure and it occurred to him that his condition could be greatly improved if there were some manner of continually removing some blood from his tume-fied veins using an apparatus where the blood could be oxygenated and carbon-dioxide removed and then be pumped back into the arteries.

Over the next three years, John talked about his idea to many people. The majority showed no interest whatsoever and few encouraged him. However, that idea of a heart-lung machine was not erased from John’s thoughts and after three years, in the autumn of 1934, he again asked Dr Churchill for an opportunity to test the viability of his ideas.

The many years of hard work, patience and persistence to develop the heart-lung machine can be divided into three stages. The first period was during the years 1934 and 1935 in the Massachusetts General Hospital in Boston, in a laboratory comprising a single room in which John and I worked without collaborators. At that time we attempted to discover if a cardiopulmonary bypass apparatus could be developed that was capable of substituting the cardiorespiratory functions of an animal while the blood was diverted from normal circulation.

The second stage of development was made in Philadelphia, in the Harrison Department of Surgical Research of Pennsylvania University, from 1936 until the Second World War interrupted the work. The most important part of this phase was focused on the survival of animals after periods of pulmonary artery occlusion while the cardiorespiratory functions were maintained by a heart-lung machine.

The third stage was developed in the Jefferson Medical College, also in Philadelphia, from 1946 until the successful operation. This stage consisted, mainly, in developing new and better methods of oxygenating blood and improving the machine with the objective of using it for human beings. Until that time, experiments had been made using cats, just
because the oxygenator did not have capacity to supply the requirements of any larger animals. Our technique gradually improved and as a consequence the animals survival also improved.

After several models and sizes of oxygenators we finally developed an oxygenator using a screen that was capable of supplying all the necessities of the animals (Fig. 1.2).

When Gibbon presented his work on successful total cardiopulmonary bypasses in cats for periods of up to 20 minutes, Leo Eloesser compared its use in human beings to the science fiction stories of Jules Verne, while Clarence Crafoord reasoned about the importance of the eventual application of the new technology in the treatment of pulmonary embolism [10].

Gibbon, using his heart-lung machine, was not successful in his first attempts at operating humans. His first three patients died; the first due to an incorrect diagnosis, the second suffered a cardiac arrest before initiating perfusion and the third presented uncontrollable hemorrhage. On his fourth attempt, to correct an interatrial communication, young Cecilia Bavolek was successfully operated by direct suture of the atrial septal defect with the perfusion lasting for 26 minutes [17,22]. The final stage of Gibbon’s work was supported by the company International Business Machines (IBM), who also provided engineers to collaborate in the development of the project [22], after a meeting with Mr. Thomas Watson, a farsighted entrepreneur and president of the multinational IBM Company. Watson had read some news about the work of Gibbon and volunteered all the human resources and materials that the surgeon deemed necessary to continue his research.

Gibbon received help from some of the most talented engineers at IBM and together they built larger machines capable of supporting oxygenation and circulation in humans. Watson himself with five other engineers from IBM worked with Gibbon on the creation of the artificial heart-lung machine. The new machine caused minimal hemolysis and contained a thermal coating which helped to maintain normal temperatures. Additionally an efficient mechanism prevented the entrance of air bubbles into the circulation as well as maintaining fine control of blood flow to keep the blood volume of the patient stable.
The first works and publications of Gibbon, starting in 1937, awakened the interest of several other researchers who, in their turn, developed similar projects [26-29].

Up to 1955, two years after the success of Gibbon, there were only five survivors worldwide who had been submitted to extracorporeal circulation [10,30]. The new technology, at first, failed to raise enthusiasm in the majority of surgeons.

Apart from being a capable surgeon, devoted researcher and professor, Gibbon possessed an uncommon knowledge of physiology, as many of his contributions with the use of cardiopulmonary bypass demonstrate, some of which are routine practices until the present days [31]. Gibbon recommended rinsing the circuit before perfusion, to remove residuals from the fabrication of the apparatus, the use of heparin and protamine to modify blood coagulation, the addition of colloids to the perfusate and to use as little perfusate as possible. Additionally, he installed audio and visual alarms in the oxygenator to help monitoring the level of perfusate. He recommended measurement of oxygen saturation in the venous blood to monitor oxygenation of patients and also recommended determination of the PaCO₂ in arterial blood to monitor the ventilatory efficiency of the oxygenator. He recommended that the mean arterial pressure during extracorporeal circulation should be maintained between 50 and 65 mmHg, which was considered sufficient for an adequate body perfusion. And, finally, he recommended that at the end of perfusion, the residual perfusate of the oxygenator should be collected and reinfused to the patient.

**OTHER CONTRIBUTIONS**

McQuiston [32] in 1950 suggested moderate hypothermia as a method to reduce the metabolic activity of infants submitted to palliative surgery for cyanotic heart diseases.

Bigelow [33,34] in 1950 demonstrated the possibility of producing total circulatory arrest under deep hypothermia in animals. He was able to resuscitate dogs after 15 minutes of circulatory arrest at temperatures between 20ºC and 25ºC.

Soon after, in 1952, Lewis and Tauffic [35], performed open-heart surgery, utilizing surface hypothermia of 30ºC and occlusion of venous return by the superior and inferior vena cavae over a period of a few minutes without any type of circulatory support. Swan, utilizing this very same technique successfully operated on a series of patients [36].

The methods of extracorporeal oxygenation at this time were unsatisfactory and the first oxygenators were not efficacious, which led some researchers to utilize the lungs of animals for the oxygenation of blood. Wesolowski, in 1952, published his experiences with animals kept on perfusion for two hours with oxygenation of blood obtained by using of dogs' lungs as oxygenators [37].

Attempts to use the lungs of different animals for extracorporeal oxygenation in hu-

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*Chapter 1 Page 8*
mans resulted in few survivors. Campbell et al. [38] used the lungs of dogs for 12 patients and obtained four survivals, while Mustard [39], utilizing monkey lungs obtained only three survivors out of a total of 28 patients. The use of heterologous lungs was soon abandoned.

Dodrill & Johnson [2], in 1953, collected blood from both vena cavae and pumped it into the pulmonary artery to allow correction of pulmonary stenosis, while the left heart maintained the systemic circulation. Their patient, although presenting with hemoptysis and pulmonary edema, recovered completely.

Researchers who attempted methods of extracorporeal oxygenation by direct contact between blood and oxygen, received a major contribution for their work when Clark, Gollan and Gupta [29] in 1950 recommended the use of polysiloxane D, a silicone polymer that removes foam and bubbles. Polysiloxane is a type of silicone capable of altering the surface tension of fluids, including blood facilitating the removal of bubbles.

Bailey [40] in 1951, described a method of extracorporeal circulation using two pumps. The first propelled the blood collected from the superior and inferior vena cavae to the lungs through the pulmonary artery and, thus, substituting the right ventricle. The second pump impelled the oxygenated blood collected from the left atrium into the systemic circulation, hence substituting the functions of left ventricle.

THE CROSS-CIRCULATION

The first ideas about cross circulation in animals emerged from the studies of Fredericq in 1890 and Hedon in 1910 [4], while the first applications in human beings dated from 1940 and 1948 by Duncan [41] and Vecchietti [42], with the objective of purifying blood of patients with renal and hepatic insufficiency, respectively.

Crossed circulation for heart surgery was experimentally studied by Kerr [43], Andreasen [44] and Southworth [45]. The latter detailed the methods and established principles for the cannulation of the system.

Andreasen and Watson [46] in 1952, working with dogs, verified that the animals tolerated about 30 minutes of occlusion of the superior and inferior vena cavae, as long as the clamping of the superior vena cava was performed above the junction with the azygous vein. Thus, only the flow of the azygous vein returned to the right heart, which could support the heart function and the life of the animal. The flow through the azygous vein is usually only 8 to 14 mL/kg/min.

Lillehei et al. [47-50] tested the viability of controlled cross-circulation in the laboratory, using low perfusion flow rates, based on the “azygous principle” of Andreasen and Watson and introduced it into the clinical practice. The venous blood of the patient was
injected into the femoral vein of a progenitor, father or mother, who functioned as an “oxygenator” and the blood of the femoral artery of the progenitor was removed for arterial perfusion of the patient. In these operations, the perfusion flow was low, about 10 to 25 per cent of the cardiac output (Fig. 1.3). With this technique, Lillehei et al. from the University of Minnesota, were able to perform numerous operations, achieving for the first time, the complete correction of interventricular communication, atrioventricular septal defects and tetralogy of Fallot [48]. The great success of cross circulation was due to the extraordinary creativity of its proponents and the excellent physical, chemical and metabolic conditions offered to the patient. The “donor” organism worked as a true “in line” monitor, capable of identifying and instantly correcting any changes in the electrolytic, acid-base, and metabolic balance, not allowing even the slightest disturbance [51]. These ideal conditions offered by cross-circulation are in-existent with mechanical cardiopulmonary bypass even in our days. Some ethical considerations, complications and deaths of donors and the development of the helicoidal oxygenator stimulated the cross-circulation technique to be abandoned. When cross-circulation was presented at a surgical congress, Willis Potts of Chicago was said to have commented, “This is the only operation that I know of that carries a potential mortality of 200 per cent” [126].

Figure 1.3. Drawing of cross-circulation developed by Lillehei and coworkers. Illustrates patient and “donor’s cannulation”. A sigmamotor pump was used for venous drainage and for pumping blood from donor’s femoral artery into an arterial cannula inserted into the left subclavian artery of the patient.

Figure 1.4. Mayo-Gibbon pump-oxygenator used at the Mayo Clinic by Kirklin in 1955.
At the same time that cross circulation was being developed by Minneapolis researchers, in the Mayo Clinic in Rochester, a few miles away, Kirklin [52] utilized a modified version of the Gibbon machine and initiated a series of successful intracardiac open heart operations. The apparatus became known as the Mayo-Gibbon oxygenator [53,54] (Fig. 1.4). During 1955 and 1956, while Kirklin used his version of the Gibbon system, which was complex, expensive and difficult to set up and operate, Lillehei used cross-circulation and, then, the helicoidal oxygenator of De Wall, which was simple, inexpensive, almost disposable and easy to set up and operate [51,55]. For some time, Minneapolis and Rochester, situated in the same state of Minnesota, were the only two cities of the entire world in which open-heart surgery was performed. Both institutions attracted surgeons from several countries, all anxious to learn the basics of this new technology, acquire the necessary equipment and devices willing to organize their own teams and apply the new knowledge in their own countries.

THE FIRST OXYGENATORS

The first attempts to oxygenate blood outside of the organism, by physiologists of the 19th century, were aimed at perfusing specific organs isolated from animals. Publications of the ideas and works of Gibbon and the possibility of building apparatuses capable of substituting cardiopulmonary functions and allowing access to the interior of a heart, stimulated several researchers to start developing oxygenators. Oxygenation and the removal of carbon dioxide at 4 to 5 liters of blood per minute for continual infusion into the arterial system of an adult patient represented an enormous challenge. Several techniques of providing oxygen to the blood were attempted with differing degrees of success enabling the development of numerous types and models of oxygenators, of which only a few had clinical application.

Gibbon described the necessity of having a thin film of blood in contact with oxygen and suggested that this would be possible by centrifugal force, the formation of bubbles in the blood or by flowing blood over a screen. He also described several problems with this process including the formation of foam, hemolysis and the production and liberation of vasoactive substances [5,9].

Initial studies with membranes for gas exchange proved the method to be relatively inefficient at oxygenation. When it became obvious that artificial circulation could be conducted with low flow rates following the “azygous principle” popularized by the Lillehei group, researches returned to study membranes as a form of producing a more physiological artificial oxygenation due to its similarity to the oxygenation achieved in the lungs. These studies originated the first generation of membrane oxygenators.
Oxygenators can be divided into three groups, according to the method employed to oxygenate the blood:

**Film oxygenators**

**Bubble oxygenators**

**Membrane oxygenators**

Film and bubble oxygenators are apparatuses in which there is direct contact of between blood and gas. In membrane oxygenators, blood and gas circulate separated by a membrane that is traversed by gases in both directions, according to their concentrations.

**FILM OXYGENATORS**

Film oxygenators create a large surface area for gas exchange by distributing a quantity of blood in relatively thin layers. Most of the oxygenators used at the start of extracorporeal circulation were of this type. In these oxygenators the venous blood is distributed in fine films on a support exposed to an oxygen-rich atmosphere.

The thickness of a blood film formed on a solid surface is greater than the diameter of pulmonary capillaries. The great difference in surface tension between gases and blood, the prolonged contact time and some turbulence in the blood flow due to the oxygenator favor oxygenation and the elimination of carbon-dioxide [4,56,57]. The blood may be distributed over different types of surfaces, including screens, cylinders, cones or discs. These oxygenators are commonly classified according to the type of support utilized for the blood film. The main oxygenators of this type are cylinder oxygenators, screen oxygenators and disc oxygenators.

**CYLINDER OXYGENATORS**

The revolving cylinder of von Frey & Gruber may be considered the forerunner of cylinder oxygenators. The venous blood was spread on the internal surface on the cylinder through which a current of air or oxygen circulated.

Karlson [56,58], in 1949, worked with cylinders placed in vertical and horizontal positions without having appreciable success. Kunlin [59], in 1952, associated several cylinders to increase the surface area for gas exchange. Crafoord, Norberg and Senning [60], in 1957, built a revolving cylinder oxygenator that consisted in a reservoir containing six cylinders, which revolved around a central axis. The reservoir received venous blood siphoned by gravity. The rotation of the cylinders favored the forming of a film of blood where gas exchange took place. These oxygenators were never really used much in clinical practice.
SCREEN OXYGENATORS

In these oxygenators venous blood flows over a support, similar to a picture frame containing a canvas. The first oxygenator successfully utilized by Gibbon, consisted of vertical screens onto which venous blood was slowly poured. The blood ran down the screens forming thin films of blood on both sides of the screen. Oxygen circulated between the screens enabling gas exchange. The system was complex and included a pump which recirculated the blood within the oxygenator to improve oxygenation. One pump was used to drain the venous blood while another pump made arterial infusion [5,7,9,55].

In 1955, researchers led by Kirklin & Jones perfected the original design of the Gibbon oxygenator which was utilized for a large series of surgeries [52-54,61].

DISC OXYGENATORS

In disc oxygenators, a set of metallic discs mounted on a horizontal axis spin inside a glass cylinder, in which the blood circulates. As the disc rotates, its surface becomes lined with a thin layer of blood which is then exposed to oxygen while the disc completes its rotation.

Bjork [62] in 1948, working in the laboratory of Crafoord in Switzerland built the first disc oxygenator. However, Kay & Cross [63] in 1956 proposed a more efficient disc oxygenator. The oxygenator had 59 12.2 cm discs separated by 5 mm gaps. The discs were lined with Teflon and the surface was siliconized. The cylinder was made of Pyrex with a length of 33 cm and diameter of 13.3 cm. The discs rotated at a velocity of up to 120 rotations per minute. The venous blood entered at one side of the Pyrex cylinder and the oxygen entered at the opposite side (Fig. 1.5).

Soon after in 1957, Kay [64] modified the surface of the discs, making them rough, which increased the surface area of the blood film on the discs as well as produced turbulence, thereby increasing gas exchange. These oxygenators became very popular and
were very much used until the start of the 1970s.

**BUBBLE OXYGENATORS**

The concept of introducing oxygen into the blood by the formation of gas bubbles is very old and was already known by Schröeder in 1882. Some authors, tried to design oxygenators for human surgeries based on this principle. However, there were problems, such as, how to remove the foam and gas mixed in the blood before arterial re-infusion. These problems were only overcome after the introduction of silicone in the 1950s.

Between 1950 and 1952, Clark [65] manufactured his bubble oxygenator; in truth, the first prototype of this type of oxygenator. It consisted in a chamber for bubbling made of siliconised glass containing an oxygen dispersion system also made of porous glass with two entrances to facilitate the control of oxygenation and variations in the pH of the blood by adjusting the quantity of carbon-dioxide removed by the apparatus. That first chamber was connected to a second in series, in which a vacuum of -90 mmHg helped to remove excess gas and bubbles. In this chamber the blood passed through a web of Teflon strips lined with silicone, where the bubbles burst. Following this, the blood entered an arterial blood reservoir altered depending on the patient’s weight. This oxygenator was successfully used and served as a model for several others based on the same principles of oxygenation (Fig. 1.6).

In 1956, De Wall [66-68] described his very efficient helicoidal oxygenator that took advantage of the concept of de-bubbling using silicone. His sequential design favored the construction of the apparatus using resources available at that time. This oxygenator consolidated the principles of artificial oxygenation using the bubble method and served as the basic model for several other oxygenators; it was easily built and either sequential or concentric. This basic model prompted a rapid increase in heart surgery in the 1970s (Fig. 1.7). De Wall’s oxygenator basically consists of three chambers connected in series, for
which reason the model is called sequential:

- Oxygenation chamber
- De-bubbling chamber
- Arterial reservoir

Venous blood enters into the oxygenation chamber by the venous inlet, in the lowest section of which there is a multi-perforated flat disk, called the oxygen dispersal system which produces fine jets when oxygen is injected below the disk. The oxygen jets in the venous blood column form bubbles, at the surface of which oxygenation and elimination of carbon-dioxide takes place. The contents of the oxygenation chamber are transferred to the de-bubbling chamber where bubbles are destroyed. The blood returns to the liquid phase and any excess of gas is removed from the apparatus. The oxygenated and de-bubbled blood is filtered in the de-bubbling chamber and gently runs into the arterial reservoir whose helicoidal form helps to trap any remaining bubbles. The bubbles that reach the reservoir tend to float in the up most spirals of the helicoidal reservoir. The outlet of the reservoir is connected to a positive displacement pump.

An important characteristic of the De Wall oxygenator is its simplicity. Its construction with easy-to-find materials allows its disposal, eliminating problems of cleaning and re-sterilization. Lillehei, De Wall and Gott [69-71] perfected the helicoidal oxygenator and directed its evolution as an industrialized disposable product manufactured by the American company, Travenol. Units were supplied in sterile, ready-for-use, packages, similar to current oxygenators. Its last version consisted in two sheets of polyvinyl bonded together which delineated the outline of the oxygenator (Fig. 1.8).

In 1956, Rygg & Kyvsgaard [72,73], in Denmark, in collaboration with the company Polystan, built a model of a disposable oxygenator which was very popular in Europe. It consisted of two sheets of polyethylene bonded together, as in the De Wall and Lillehei oxygenator, delineating the different chambers of the oxygenator. Oxygen was introduced through a perforated tube directly into the oxygenation chamber and at the top of this chamber there was a set of siliconized polyurethane sponges that burst bubbles and re-
leased any excess of gas. The oxygenated blood ran to a 2nd chamber to settle and from this to the arterial reservoir.

Concentric bubble oxygenators

It was Gollan [74] who had the idea of making oxygenators more compact, placing the different components inside each other, producing the design that is adopted until today. This arrangement made oxygenators smaller and easier to set up and use. Gollan also included a glass spiral inside the oxygenation chamber which functioned to modify the temperature of the blood using circulating water (Fig. 1.9). Soon after, Cooley [75,76] built a concentric bubble oxygenator entirely of stainless-steel which was easier to clean, sterilize and set up and was very resistant to impact. A plastic ‘U-shape’ tube connected to the arterial reservoir served as a level monitor of the blood in the oxygenator during use.

The main advantages of this arrangement, with oxygenator chambers inside each other, were a reduction in the size of the apparatus and in the volume of perfusate required, a reduction in the contact of blood with foreign surfaces and less heat loss to the environment.

Bubble oxygenators today are all based on the general principles developed by Clark, De Wall, Lillehei and Gollan.

MEMBRANE OXYGENATORS

Studies on artificial oxygenation through direct contact of gas and blood ran into problems because of the formation of bubbles and foam which were difficult to remove. Some investigators tried membranes, which were permeable to gases, to make a physical barrier between the blood and gas. This method prevented the formation of blood bubbles and made artificial
oxygenation more similar to what occurs in the lungs.

In 1944 Kolff [77] observed oxygenation of blood through cellophane chambers of his first artificial kidney and started a series of studies aimed at utilizing this material as a gas exchange membrane. Barrer [78] and van Amerongen [79] demonstrated that some natural and synthetic elastomers were also permeable to gases.

Other researchers demonstrated that the passage of gases through semi-permeable membranes occurred by diffusion. The gas is absorbed into the surface of the membrane, passes through the membrane in solution on of its material and is released on the opposite side of the membrane [80,81]. Several materials were tested in respect to their permeability to gases in an attempt to identify the most appropriate for artificial oxygenation [82,83].

Hopf [84] demonstrated that placing membranes between the gas and blood caused less damage to red blood cells, leucocytes and platelets. Owens [85] and Lee [86] observed less denaturation of fat and proteins.

The thickness of the film of blood to be oxygenated is one of the greatest difficulties when designing membrane oxygenators, due to the additional obstacle, represented by the membrane, in the passage of gases to the blood. Additionally, the selection of the material for the membrane is critical. The material should be harmless to blood; should be available in very thin sheets without loss of resistance and should have a great permeability to oxygen [87].

Although diffusion of carbon dioxide in the respiratory membrane of the lung is much faster than of oxygen, the first membranes utilized in oxygenators had much difficulty in removing CO₂ from blood. Large surfaces were necessary to enable an efficient elimination of the gas.

The development of membrane oxygenators was considerably slower and more complex than the other types of oxygenators. These projects involved some arduous stages such as the selection of the membrane and checking its compatibility with blood, its permeability to respiratory gases, the design of routes for blood and gas between the membranes with minimum resistance to the flow of both and the development of efficient mechanisms to distribute the blood in thin layers, as well as to impede mixing venous blood with blood already oxygenated.

Kolff [88] in 1955 tested the first successful prototype of a membrane oxygenator from polyethylene sheets in an experimental laboratory. The membranes were rolled around a central axis giving the oxygenator the format of a coil.

Several other researchers created different models of membrane oxygenators, using the best materials at that time for gas exchange, including cellophane, polyethylene, cellulose, silicone and Teflon [21]. Klaus and Neville [89] were the pioneers to use mem-
brane oxygenators for clinical heart surgery in 1958. They published a series of cases that were operated on using their apparatus (Fig. 1.10).

The membranes were flat, made of Teflon and placed in overlapping layers. The oxygenators were large, difficult to set-up and frequently presented leaks. Following this, other membrane oxygenators were used by Bramson [90], Peirce [91], and Landé-Edwards [92], whose configurations were similar to the initial project of Clowes and Neville. The first membrane oxygenators required from 3 to 6 m² of membranes for adequate gas exchange.

Kolobow in 1965 [93] used a configuration similar to Kolff for his oxygenator. Long strips of silicone were supported with spacers that impeded the collapse of the membranes. The blood flowed inside the strips and the oxygen circulated towards the central axis that supported the spool of membranes. This model worked adequately for long periods of time and was adopted for procedures that used ventilatory and circulatory support. The oxygenator of Kolobow was developed and perfected. Nowadays this model is produced under different brand names due to fusion and incorporation of some companies by larger companies, although it still maintains its characteristics and indications. It is the most indicated oxygenator for long procedures.

First generation membrane oxygenators had a common characteristic that there was much resistance to the passage of blood along the membranes which simple siphoning could not overcome. Some devices were set up on the positive pressure side of roller pumps, while others required an additional pump to circulate the blood in the membrane compartment. Due to the difficulty of gas exchange and the complexity to build and use them, first-generation membrane oxygenators were not very popular. Development of technology to produce expanded and capillary membrane oxygenators, favored the appearance of the current generation of these oxygenators.

HEAT EXCHANGERS

The loss of heat from the blood because of the large surface areas represented by the oxygenator and the extracorporeal circuit was already considered by the pioneers of this
technology. The temperature of the blood was maintained within the normal range by utilizing several artifacts, among which were immersion of part of the oxygenator in warm water [94,95] and the utilization of infra-red lights [96] which was used with disc oxygenators. These methods of temperature regulation, although rudimentary, were sufficient to compensate for heat loss and adequately served artificial circulation in the 1950s.

Exchange units, with capacity to remove from or supply heat to the blood, were developed during the first years of extracorporeal circulation. It was Gollan [74,97] who, in 1952, had the idea of introducing a spiral, initially made of glass and later of silver, inside his concentric bubble oxygenator with the objective of inducing hypothermia and its reversal during artificial circulation.

Ross [98] in 1954 created a double concentric spiral in which the blood circulated inside the internal spiral with water circulating inside the external spiral. Zuhdi [99] in 1960 took advantage of the principle described by Ross using the helicoidal oxygenator of De Wall, in which he used hypothermic perfusion at low arterial flow rates.

In 1958 Brown et al. [100] worked in conjunction with the Harrison Radiator Division in General Motors and designed the Brown-Harrison heat exchange unit, an isolated unit that could be used with any oxygenator as it was connected to the arterial or venous line. The Brown-Harrison heat exchange unit consisted of a 38cm-long stainless steel cylinder which surrounded a bundle of tubes also made of stainless steel in which the blood circulated. Water circulated around these tubes inside the cylinder. Water and blood circulated in opposite directions to increase the heat exchanger. This heat exchanger unit was extensively utilized and was the basis of other types of devices (Fig. 1.11). Due to its efficiency, it was adopted as the gold-standard to assess the performance of other heat exchanger units in extracorporeal circuits.

Urschell [101] in 1960 described a heat exchanger unit to use inside the glass cylinder that contained venous blood of disc oxygenators. Two parallel tubes supported tubular
"bridges" in the form of a segment of a circle or horseshoe inside which water circulated.

Reports of heat loss in extracorporeal circulation and the necessity of manipulating the gas exchange was the origin of numerous devices constructed for use either in isolation or in conjunction with oxygenators. Three general types of heat exchange units were developed.

The first type consisted of a water chamber that surrounded the oxygenator column of bubble oxygenators. The chamber had independent inlets and outlets however there was no internal circuit for the water. It functioned as if the oxygenator column was immersed in a bath of hot or cold water. This corresponds to the principle described for thermal-regulation in the first oxygenators. It was commonly used in the 1970s with the reusable oxygenators but it was soon abandoned due to its low efficiency.

The second type is based on the principles of the parallel tube exchange unit of Brown-Harrison, which consisted of tubes made from materials with good heat conduction properties, in which the blood and water circulated on opposite sides and in opposite directions, favoring heat exchange. Initially they were constructed as isolated units to be used on arterial or venous lines and later they were incorporated in several oxygenators, including disposable devices. This was an extremely efficient method of heat exchange. The W. Harvey oxygenator was extremely efficient and popularized the original system of Brown-Harrison, in which the blood circulated inside elliptical parallel tubes. In other oxygenators, which used the same principle, the water circulated inside parallel tubes (Fig. 1.12).

The third type corresponds to variations of the Gollan spiral heat exchanger unit, which is also constructed from several materials with good heat conduction properties. The size and general shape vary to adapt to the format of the chamber in which they are immersed. In all cases in which the heat exchanger unit is part of the design of the oxygenators, they have a secondary function of reducing the amount of priming necessary to use the apparatus.

The water flow necessary for the heat exchange is much higher than blood flow rates.
making the pressure of water inside the heat exchange units greater than the pressure of the blood. Thus, leaks that occur during heat exchange are extremely serious, as contaminated water invades the blood. Esmond [102] in 1959 postulated that adequate heat exchange units for artificial circulation should have soldered joints only on the external part of the body of the oxygenator in order to avoid leaks which may contaminate the blood.

With the search for new and more efficient materials, the smooth surface of the spiral walls became corrugated, which greatly increased the surface area available for heat exchange as well as producing turbulence at the interfaces with both the blood and water which also increased the efficiency of the heat exchange units.

The majority of heat exchange units used for extracorporeal circulation have the capacity of reducing the nasopharyngeal temperature by 1°C to 3°C per minute, in individuals perfused with blood flows between 1 and 4 L/minute. Rewarming in any type of heat exchange unit is always slower than cooling.

MECHANICAL PUMPS

Mechanical pumps for artificial circulation of blood were adapted from existing models and projects used in fluid engineering. Some pumps were copied from those first utilized by physiologists however they were incapable of pumping large volumes of blood. During a long time there was a search for systems able to pump large volumes of blood at an average flow rate of 1 to 5 liters per minute without causing appreciable injury to cellular and proteic elements of blood. Pumps initially employed by physiologists could only impel small quantities of blood. Injury caused to blood elements was so great that after short perfusion times the vascular bed lost its reactivity [4]. The most important factor involved with the destruction of blood elements was the flow velocity. The pump is the point in the circuit that transfers energy from moving mechanical parts to the blood. A pump considered adequate should be capable of impelling blood at pressures of up to 180 or 200 mmHg with adjustable volumes and frequencies and maintain a direct relationship between the frequency and emitted flow.

The search for the first pumps for extracorporeal circulation raised controversy between the advantages and disadvantages of continuous and pulsating flows. Some authors, including Jongbloed [103] and Wesolowski [104] after studying the two types of perfusion, pulsatile and non-pulsatile, concluded that there was no difference in the reactivity of the cardiovascular system, the function of the organs remained intact and the prognoses of animals after perfusion were essentially the same. Ogata [105] and Nonoyama [106] after similar studies concluded that with the absence of pulsatile flow, the pressure tended to be lower and there was a greater tendency to develop metabolic acidosis and
edema, as well as an irregular distribution of the blood to the visceral region. This deterioration would be associated to dysfunction in the peripheral circulation caused by non-pulsatile flows. This controversy still exists.

Aiming at maintaining the blood flow constant, the search for adequate models concentrated on those that presented an occlusion mechanism, as the output could be maintained easier, independently to other factors.

In general the pumps can be classified according to the mechanism of the moving parts that transmit energy to the liquid. By these criteria the pumps are classified in two main types: centrifugal and positive displacement pumps. Centrifugal pumps are those in which the propulsion action is by transmission of energy by the rotation of a propelling element. Positive displacement pumps are those that propel the liquid progressively from an orifice of suction to an orifice of discharge.

With reciprocal pumps, similar to the heart, alternating movements propel the fluid. The suction and release valves close the orifices of a chamber that is subjected to the reciprocal action of a piston, compression bar or diaphragm.

Among the diverse types of positive displacement pumps considered for use in extracorporeal circulation, there is an application for revolving roller pumps, multiple-finger pumps and reciprocal pumps similar to those of the ventricle. In positive displacement pumps, the capacity of the pump depends on volume of liquid displaced with each movement and the number of displacements per minute. Some characteristics of the pumps, such as the turbulence caused, the force of compression, stagnation points of the blood flow and the production of heat due to friction of moving parts are important in the choice of a pump for extracorporeal circulation.

Dale & Schuster [107] in 1921 created a pump capable of producing a pulsating flow moved by piston. The blood flow was controlled by the presence of valves and utilized a hydraulic system for pumping. It was a diaphragmatic type pump manufactured from synthetic rubber and plastic.

In 1954, Lillehei and his group, jointly with engineers from the University of Minnesota, developed a positive displacement pump, the Sigmamotor pump, which was much used in heart surgery with artificial circulation together with the De Wall oxygenator. This pump consisted in a set of bars or “fingers”, which successively compressed a flexible tube, from the inlet to the outlet, propelling the blood inside the tube. The Sigmamotor pump made use of its great popularity at the start of artificial circulation and was later substituted by the roller pump, mainly due to the trauma caused to the blood elements [48,51].

Roller pumps are not a new invention. Even though their invention is frequently attributed to De Bakey, in truth, this type of pump was patented in 1855 by Porter & Bradley [108] as a rotary pump. Following this, the original idea underwent many modifications up
to the design of De Bakey [109] in 1934 as a pump for blood transfusion. The principle of rotating rollers was tested for extracorporeal circulation pumps by several authors [110]. Shaw [111], Melrose [112], Rygg [113] and Kirklin [114] in their Mayo-Gibbon apparatus, utilized a single excentric roller whose rotation compressed a flexible latex tube. Lenfant [115] and Battezzti [116] created a model of a pump utilizing three rotating rollers that proved to be excessively damaging. The design by De Bakey with two rollers and modified by several other authors, including Leonards & Ankeney [117] acquired great popularity and became universally adopted for extracorporeal circulation and other applications that involve pumping of blood such as hemodialysis and ultrafiltration (Fig. 1.13).

![Figure 1.13. Roller pumps. A. Single excentric roller pump used in the Mayo-Gibbon heart-lung machine. B. Double roller pump, adopted for general clinical use. C. Three roller pump; excessively traumatic to blood.](image)

Although the principle of centrifugal pumps is old in fluid engineering, only recently pumps of this type have been developed for use in extracorporeal circulation.

**EVOLUTION OF MATERIALS**

The choice of materials for the manufacture of artificial circulation devices has always been a great challenge. The characteristics of internal lining of the cardiovascular system and all its properties can not be simulated by any known substance. Contact of the blood with the different foreign surfaces of pumps, oxygenators, tubes, connectors and cannulae demands much research to find the best material for each situation [118,119]. Initial research with artificial circulation demonstrated that the materials for use in contact with blood, should not react chemically with any of its elements; should be resistant to impact and corrosion; should be impermeable and permit high polishing in order to reduce friction during blood circulation. Other characteristics such as cost and availability were also important considerations. Many materials were rejected after practical experimentation.

Glass and rubber were the first materials considered adequate to remain in contact
with blood. Parts of the equipment requiring resistance and rigidity were made of metal. Some noble metals such as gold and silver were considered adequate however their cost was prohibitive. Even so, silver has been used for heat conductivity in heat exchanger units. Diettert [120] in 1958 introduced aluminum for the manufacture of some components however its acceptability was delayed. Stainless steel soon became very popular, especially as it could be easily molded and polished, for the manufacture of several components including parts for reusable oxygenators. Steel is an alloy of chrome and nickel. Steel normally can not be magnetized and can be easily washed using detergents without causing corrosion and is sterilized by any method, chemical or physical. It became very popular before the time of disposable apparatuses. Aepli [121] studied several metals in contact with blood, including copper, bronze, nickel and steel until they concluded that steel is the best for biological applications.

Other extensively used materials were glass in spite of its low resistance to impact, silicone rubber, latex, nylon, Teflon, and some polyvinyl polymers.

The tubes of the circuit were made of polyvinyl and its different polymers, a group of transparent plastic materials with excellent properties for this application. Polyethylene was also commonly used. The manufacture of tubes using the extrusion technique was most favored for polyvinyl products, of which tygon seems to be the best formulation.

Among the rigid plastics, acrylic was the least used and polycarbonate the most commonly employed; this is the main raw material of the majority of modern oxygenators.

FILTERS AND BUBBLE TRAPS

The complications observed in the initial experiments and clinical applications of extracorporeal circulation, encouraged the development of additional devices for the circuit. Emboli, in particular, were an important reason to create filters and bubble traps.

The equipment often causes the formation of platelet and cellular aggregation; blood clots and cellular debris are suctioned from the operative field and oxygenators release excessive silicone. Moreover, not uncommonly, de bubbling was incomplete and bubbles or foam entered the arterial chamber of oxygenators. To minimize these difficulties, filters and bubble traps were developed.

With the expansion of artificial circulation procedures, a higher incidence of postoperative complications involving vital organ function was noted. These alterations affected the lungs, kidneys, liver and the central nervous system and were not very well understood. It was believed that these complications were due to alterations of blood elements caused by injury sustained in the extracorporeal circuits and they resulted in microvascular occlusion. Often clinical symptoms were not noted, although pathological findings in-
icated the presence of microvascular occlusions. Aggregations of leukocytes, platelets and red blood cells, denaturation of proteins and the appearance of diverse particles of fats, fibrin and gaseous microbubbles were identified [21,122].

Filters were created aiming at holding emboli within the extracorporeal circuit, impeding their transportation to the microcirculation of the patient. The first filters created offered much resistance to the blood flow and were not very practical to use, as well as making air removal from inside the filter difficult [4,21,123].

The first filters were made from stainless steel or nylon mesh and the useful area of the filter was calculated to be around 35 to 65% of its total area. Taylor in 1959 demonstrated that a surface area of about 50 cm² for each liter of blood gave an acceptable safety margin for a filter even with some obstruction due to retention of fibrin and platelets [21] (Fig. 1.14).

From the start of developing filters, the ideal position in the circuit has been discussed, with Senning & Gross [4,21] suggesting the best position is the arterial line, between the pump and the arterial cannula. They also demonstrated that a filter on the cardiotomy line may retain fragments of tissues and cellular debris.

In 1960 Landew after studying emboli, reported that 2.2 mL of air in the arterial line in the form of microbubbles is sufficient to cause severe neurological injury [124].

The general principles to eliminate air from the circuit were developed by Clark in 1956. De Wall et al. on recognizing those principles, developed their helicoidal reservoir, in which the upper spirals retained any bubbles that might reach in the reservoir [4,16,21,122].

The first bubble traps were frequently used in extracorporeal circuits. Subsequently, the functions of the filters and bubble traps were combined in a single device resulting in a new generation of filters with varying capacities and efficiencies but becoming more sophisticated with different layers of materials with decreasing porosity and with specific parts to eliminate air and bubbles.

Cardiopulmonary bypass systems continue to evolve, with more and more velocity. New knowledge and new devices and equipment are designed and perfected and each one in its turn, contributes to the growth of this important area of work within heart surgery and other areas of healthcare.
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