History of Cardiac Transplantation: Research, Discoveries, and Pioneers

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Introduction

Medical innovations are fueled by disease and premature death. Except for 1918 when influenza claimed more lives, cardiovascular disease has been the number one cause of death in the US every year since 1900 [1–3]. Furthermore, congenital heart disease (CHD) is the most prevalent genetic disease of live-born children [3, 4] (Figs. 25.1 and 25.2). Cardiovascular and CHD can progress to end-stage heart disease, and the only definitive therapy for advanced heart failure is heart transplantation.

Through the work of many innovative surgeons and scientists, heart transplantation has become commonplace [5–7]. Pivotal inventions such as cardiopulmonary bypass and the refining of anastomotic techniques made heart transplantation technically possible. The development of preservation solutions and effective immunosuppression regimens made heart transplantation successful [7]. This chapter reviews the research, experiments, and technology that led to modern-day heart transplant surgery.

Fig. 25.1 Congenital heart disease is the most common genetic defect. C. Walton Lillehei, MD, examines a child with congenital heart disease requiring corrective surgery and temporary pacemaker support. Photograph SEPS licensed by Curtis Licensing, Indianapolis, IN. All rights reserved.

Fig. 25.2 Congenital heart disease is the most common genetic defect. Children with congenital heart disease were hospitalized for long periods of time and received visits from entertainers who would visit the patients in the hospitals

Early Innovators and Cardiovascular Medicine

In the early 1900s, many considered the repair of blood vessels an impossibility. Alexis Carrel, MD (June 28, 1873–Nov. 5, 1944), led the way in small vessel vascular surgery, which promoted organ transplantation [6]. As a medical student, Carrel first became interested in vascular anastomosis after the president of France died from a laceration of the portal vein. At the time, the death of the president was believed inevitable because the procedure to repair blood vessels was unknown [6]. Dr. Carrel reviewed experiments by Mathieu Jaboulay that involved the repair of divided carotid arteries with an everting mattress technique. This technique was not reproducible on small vessels so Carrel began working on vascular anastomotic experiments and published a manuscript on his technique in 1902 [5, 6].

After he experienced a minor setback in his medical career, Dr. Carrel moved to Chicago in 1904 and began work with Charles Guthrie, MD (Sept. 26, 1880–April 1963), at the University of Chicago [5–7]. There he refined his triangulation method of vascular anastomosis using fine needles and sutures treated with petroleum jelly. While at the University of Chicago, Drs. Carrel and Guthrie demonstrated that veins could be used as a viable substitute for arteries by replacing sections of carotid artery with the jugular vein [5, 6]. They also proved that a vein patch could tolerate arterial pressures. Using these techniques, they published a manuscript in 1905 detailing the successful transplantation of a dog's kidney into the neck of another recipient dog using these refined surgical skills [5, 6]. The kidney functioned normally after transplantation; however, the dog died later of infection. Drs. Guthrie and Carrel subsequently transplanted the thyroid gland, kidneys, and ovaries from one dog to another as well as the heart of a small dog into the neck of a larger dog with witnessed contractions following implantation.

In 1906, Dr. Carrel moved his research to the Rockefeller Institute in New York [6]. There he established that blood vessels could be preserved in cold saline for days to weeks, reimplanted, and maintain their function. This was his entry into experiments on tissue preservation—so important in organ transplantation. Dr. Carrel pursued different methods of tissue and organ preservation such as heating and dehydration and storing tissues in glycerin, formalin, or petroleum jelly. By 1909, Dr. Carrel had successfully transplanted other organs in animals, such as the adrenal gland, spleen, intestine, heart/heart-lung block, and limbs [5, 6]. His groundbreaking work focused on transplantation earned him the Nobel Prize in 1912.

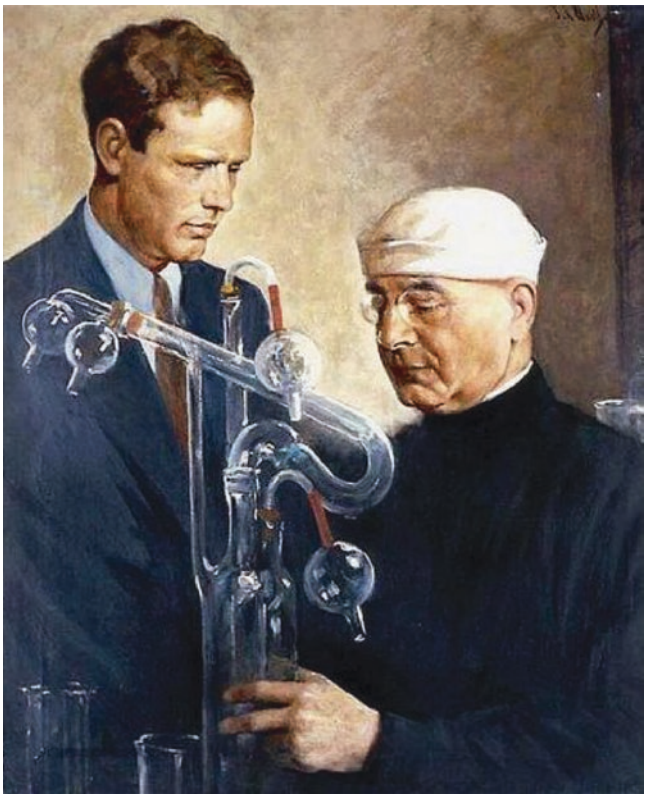

Fig. 25.3 Early research initiatives focused on the pump oxygenator. The famous aviator Charles Lindbergh worked with Nobel Prize winner Alexis Carrel in the laboratory

In 1929, he developed protocols for organ perfusion. These initial experiments failed due to infection of the perfused organ. With the aid of renowned pilot Charles Lindbergh (Feb. 4, 1902–Aug. 26, 1974), who became a close friend and colleague, Dr. Carrel developed the first functional pump oxygenator 5 years later [5–7]. Together, Dr. Carrel and Lindbergh coauthored a book, *The Culture of Organs*, and they appeared on the cover of Time magazine (1938) (Fig. 25.3).

Early Description of Graft Rejection

In the 1930s, Frank Mann, MD (Sept. 11, 1887–Sept. 30, 1962), uncovered allograft rejection by examining failing heart transplants in animal models [8]. His seminal studies with heart transplantation examined implantation of the denervated heart of dogs. He found that the transplanted heart began to beat after coronary blood flow was established. The donor heart survived an average of 4 days [8]. The longest survival was 8 days. He noticed that every graft failure was caused by cardiac distention before a rhythm was established. Therefore, graft protection included avoidance of air embolism and ventricular distention. Once the donor heart was at the end of its lifespan, Dr. Mann examined the removed heart and found [5, 8]:

» *The surface of the heart was covered with mottled areas of ecchymosis; the heart was friable on section. Histologically the heart was completely infiltrated with lymphocytes, large mononuclears and polymorphonuclears… it is readily seen that the failure of the homotransplanted heart to survive is not due to the technique of transplantation but to some biologic factor which is probably identical to that which prevents survival of other homotransplanted tissues and organs.*

This observation would later prove valuable to our understanding of graft rejection and immunosuppressive therapy.

Parabiotic Perfusion

Twenty years later, at the Chicago Medical School, work on another piece of the puzzle started to progress: graft preservation [5, 9, 10]. Drs. Marcus, Wong, and Luisada tried using a third dog to support the donor heart until implantation [5]:

» *The method we have called interim parabiotic perfusion; it is a homologous extracorporeal pump.*

Unfortunately, the donor heart only survived 48 h. Another group from Hahnemann Medical College—Drs. Wilford Neptune, Charles Bailey, and Brian Cookson—also made strides in 1953 toward graft preservation [5, 7]. They used hypothermia of the donor heart, but only achieved a 6-h survival time when transplanting both the heart and lungs into dogs.

World's First Orthotopic Heart Transplant in an Animal

Although Dr. Vladimir Demikhov's work was not available in English until the early 1960s, Demikhov (July 18, 1916–Nov. 22, 1998) began making advances in heart transplantation in the late 1930s [5, 7, 10]. As a student in 1937, he engineered the first mechanical assist device and was able to support the circulation of an animal for 5.5 h with the heart excised. Due to WWII, there was a break in Demikhov's research, but in June 1946, he performed a heterotopic heart-lung transplant in an animal thorax. The animal survived 9.4 h. In 1951, he performed the first orthotopic heart transplant in an animal. Through the mid-1950s, he completed 22 orthotopic heart transplants without cardiopulmonary bypass by using sequential anastomoses to maintain perfusion throughout the procedure [5].

During one of his experiments in January 1955, he ligated the recipient's great vessels and closed the mitral valve so the recipient was exclusively dependent on the transplanted heart. The dog survived for 15.5 h. Death was secondary to thrombosis of the superior vena cava. From 1946 to 1958, Vladimir Demikhov performed 250 heart transplants in animal models, achieving survival up to 30 days [5]. Before his

death, Demikhov was awarded the Pioneer Award by the International Society for Heart and Lung Transplantation for his innovations in the field.

Cardiopulmonary Bypass

Thanks to the advancements of John Gibbon, MD (Sept. 29, 1903–Feb. 5, 1973), the device known as the cardiopulmonary bypass machine (CPB) was realized [5, 7, 9]. Early in his career, Dr. Gibbon witnessed the death of a patient from a massive pulmonary embolism. While at Massachusetts General Hospital, he began engineering a machine that would take over the work of the heart and lungs during surgery [5, 7]. He continued his work after moving to the University of Pennsylvania in the 1930s. In collaboration with engineers at IBM, including engineer and IBM chairman Thomas Watson, and after many successful experiments in animal models, the first machine for human use was developed [5]. This model was a failure. A second machine was developed in Dr. Gibbon's laboratory. This iteration minimized hemolysis and the formation of air bubbles and was operational (Fig. 25.4).

The first successful use of the cardiopulmonary bypass machine (May 6, 1953) was on an 18-year-old patient with an atrial septal defect [5]. The patient survived a 26-min bypass "run" without complication. Unfortunately, subsequent operations with the CPB machine resulted in mortalities, and Dr. Gibbon then placed a moratorium on the CPB machine. Gibbon's inventions earned him the Lasker Award in 1968. John Kirklin, MD (April 5, 1917–April 21, 2004), of the Mayo Clinic along with Richard A. DeWall, MD, and C. Walton Lillehei, MD (Oct. 23, 1918–July 5, 1999), of the University of Minnesota resumed Dr. Gibbon's work and refined the CPB machine (Fig. 25.5) [11]. Secondary to their work, cardiac surgery continued to mature in the late 1950s through 1960s.

In 1959, Drs. Henry Cass and Sir Russell Brock conducted several trials focused on canine heart transplantation. The technique left atrial cuffs instead of anastomosing the cava and pulmonary veins individually. These experiments met with limited success secondary to bleeding complications [5].

The Stanford Pioneers

Norman E. Shumway, MD (Feb. 9, 1923–Feb. 10, 2006), completed medical school at Vanderbilt Medical School, his residency training at the University of Minnesota, and then his PhD in cardiovascular surgery in 1956 under Owen Wangenstein, MD (Fig. 25.6) [5, 11]. During his research training, Dr. Shumway focused his efforts on total body hypothermia, pump oxygenators, prosthetic cardiovascular grafts, and arrhythmogenesis under the direction of F. John Lewis, MD (Fig. 25.7), and Dr. Lillehei [11]. Shumway left Minnesota for California where he ultimately accepted a position at Stanford Medical Center in 1958.

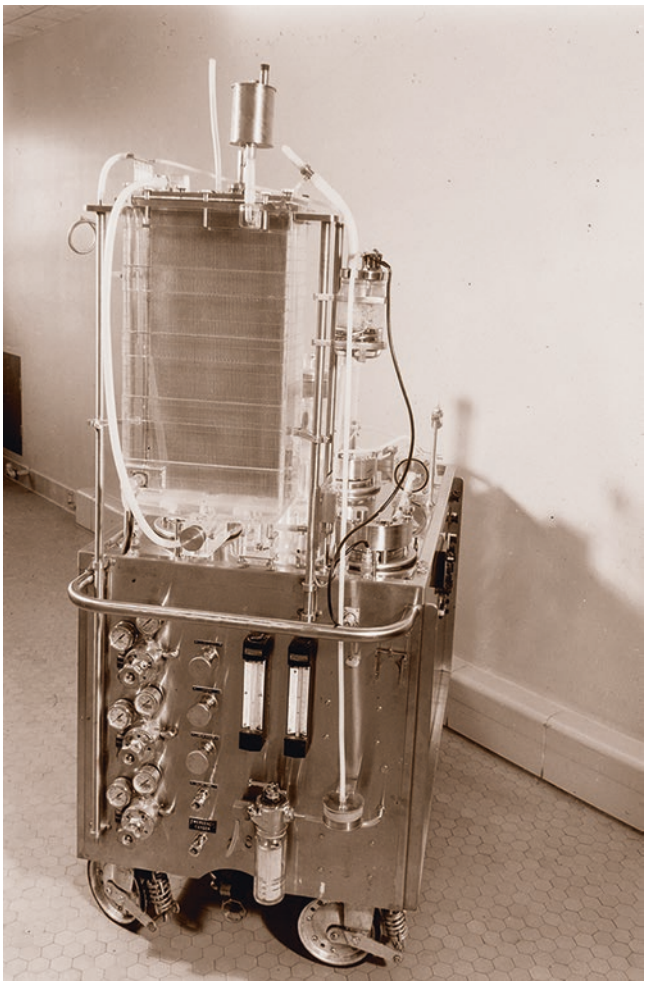

Fig. 25.4 World's first successful use of the heart-lung machine. On May 6, 1953, John H. Gibbon Jr., MD, used cardiopulmonary bypass for 26 min to close a large atrial septal defect in an adult female patient. Shown here is the Gibbon heart-lung machine (Model II), which consisted of a screen oxygenator

At Stanford, Drs. Shumway and Richard R. Lower, MD (Aug. 15, 1929–May 17, 2008), were able to optimize surgical techniques and organ preservation, and they performed the first fully successful animal model orthotopic cardiac transplant in 1959 [5]. Drs. Shumway and Lower used preservation techniques that included topical hypothermia to 4 °C with saline for graft protection and recipient protection using cardiopulmonary bypass and systemic cooling to 30 °C. Surgical techniques using atrial cuffs, previously used by Demikhov, Cass, and Brock, helped limit ischemic times to 1 h [5]. Of eight animals, five survived 6–21 days, but they quickly died from myocardial failure due to cell infiltration and interstitial hemorrhage from lack of immunosuppression [12].

» *Observation on these animals suggest that, if the immunologic mechanism of the host were prevented from destroying the graft, in all likelihood it would continue to function adequately for the normal life span of the animal.*

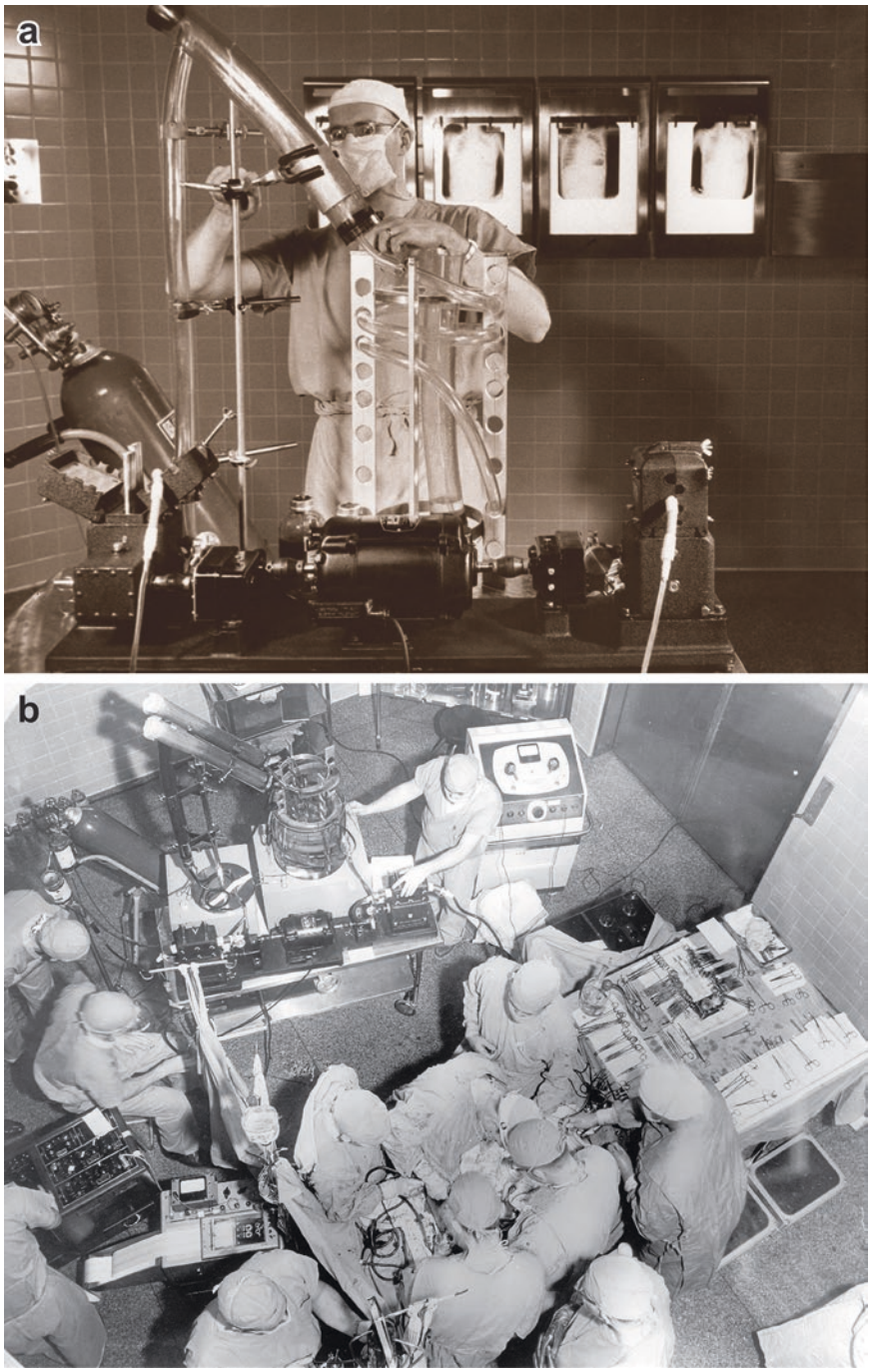

Fig. 25.5 The DeWall-Lillehei Bubble Oxygenator. (**a**) Richard A. DeWall, MD, working with C. Walton Lillehei, MD, developed an inexpensive ($15) bubble oxygenator that eliminated air bubbles. (**b**) Using the DeWall-Lillehei bubble oxygenator, Dr. Lillehei and his team performed open heart surgery to repair a patient's ventricular septal defect (May 13, 1955)

In 1961, Dr. Lower performed heart-lung transplant in canine models. Six recipients had spontaneous respirations post-implant and two were ambulatory [5]. The canine recipients died 5 days later and this was believed to be due to rejection. With continued research, it became apparent that immunologic responses were the limiting factor [12]. In 1965, Eugene Dong, MD, Dr. Lower, and Dr. Shumway found a relationship between EKG changes and rejection [5, 12]. They discovered that the EKG changes drastically improved with methylprednisolone and azathioprine, enabling one transplanted dog to survive 250 days [12].

The World's First Human Heart Transplant Using a Nonhuman Donor Organ

James D. Hardy, MD (May 14, 1918–Feb. 19, 2003), tried to promote heart transplantation in humans by way of nonhuman donors. During this time period, brain death was not accepted as end of life for a possible donor; only cardiorespiratory arrest could be used to constitute death [5, 11]. This created a conundrum in the advancement of transplantation [5, 7].

» *…The donor heart presumably would be derived from a relatively young patient dying of brain damage and the*

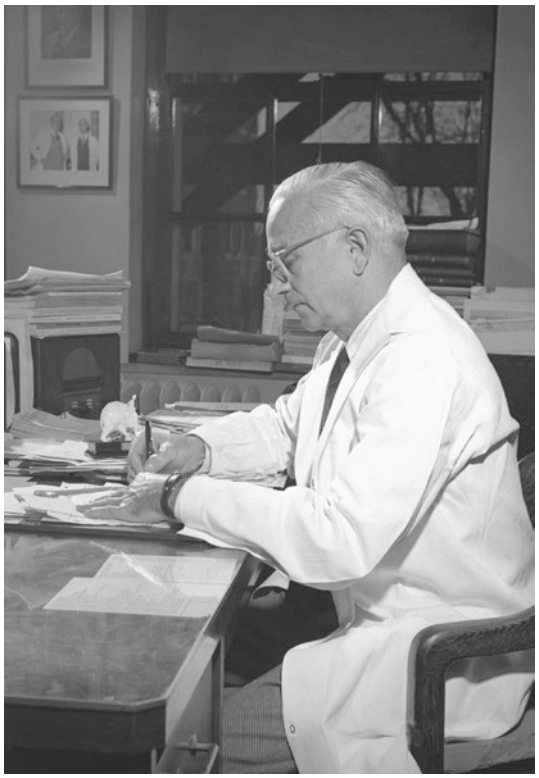

Fig. 25.6 Pioneering leadership transforms clinical practice. Owen H. Wangensteen, MD, PhD, referred to as "the Chief," served one of the longest tenures as chairman of the Surgery Department (1930–1967) and transformed the University of Minnesota surgical program, emphasizing the importance of research and its impact on clinical care of the patient

Fig. 25.7 Surgical pioneers and their impact on clinical care and the future generation of cardiovascular surgeons. F. John Lewis, MD (*right*), with Richard Varco, MD (*left*), utilized hypothermia in their open heart surgical procedures

> *recipient must be a patient dying of terminal myocardial failure… But how soon after "death" of the donor could the heart be removed?*
>
> Since we were not willing to stop the ventilator, we had concluded that a situation might arise in which the only heart available for transplantation would be that of a lower primate.

In 1964, the first human heart transplant using a nonhuman primate heart was undertaken. The first patient was a 68-year-old male with multiple medical problems, which led to a below-knee amputation, mechanical ventilation, vasopressors, and tracheostomy. At the time, there was no prospective human donor, but the dilemma with brain death again became a problem [5].

> *…for a homotransplant to succeed, the donor and the recipient must "die" at almost the same time; although this might occur, the chances that both simultaneously were very slim…Meanwhile, the condition of the prospective donor was not such that death appeared to be immediately imminent.*

Therefore, the team used a chimpanzee heart preserved by retrograde hypothermic oxygenated blood. Although the heart was implanted successfully, the cardiac output was not enough to maintain the flow needs of the patient. The patient expired in the operating room after 90 min of support by the transplanted heart. Dr. Lower performed one experiment that was similar to the experience of Dr. Hardy. He transplanted a cadaver heart into a baboon; the animal died due to elective termination of the experiment.

The World's First Successful Heart Transplant

Christiaan N. Barnard, MD (Nov. 8, 1922–Sept. 2, 2001), performed the first human-to-human heart transplant on Dec. 3, 1967, at Groote Schuur Hospital in Cape Town, South Africa (Figs. 25.8 and 25.9) [5–11]. Originally trained in renal transplantation under David Hume, MD, and Dr. Lower, MD, Dr. Barnard ultimately wanted to perform heart transplantation (Table 25.1).

The desire to pursue heart transplantation was primarily influenced during his 2-year research program at the University of Minnesota, where he interacted extensively with Dr. Shumway [11]. Having returned to Cape Town, South Africa, in 1958, Dr. Barnard resumed his research. He performed 48 transplants in dogs using techniques he learned in renal transplantation. Dr. Barnard is credited with the second successful renal transplant in South Africa in 1967. (The world's first renal transplant was performed in 1953.)

This research experience, the emergence of new surgical techniques by Drs. Shumway and Lower (then at Stanford), and renal transplant experience provided the platform for the world's first successful human cardiac transplant [5]. Louis Washkansky, age 53, a local grocer, was the first human recipient (Fig. 25.9). He suffered from ischemic heart disease; the donor was a brain-dead victim of a motor vehicle

accident the day before (Dec. 2, 1967). The donor was placed on cardiopulmonary bypass after the absence of EKG activity and spontaneous respirations were declared. Ischemic time was 21 min [5].

With a transplant team of more than 30 healthcare providers, the transplant was successfully performed (Fig. 25.8, Table 25.1). The immunosuppressive treatment at the time consisted of azathioprine, local irradiation, and prednisolone [12]. Unfortunately, the recipient was suffering from pseudomonas cellulitis at the time of transplant. Although he was given appropriate antibiotics, he died 18 days later due to pseudomonas and Klebsiella pneumonia [5]. Dr. Barnard had more success with his second attempt (Jan. 2, 1968) at heart transplantation with the recipient, Philip Blaiberg, MD, surviving 19 months. Further enthusiasm for cardiac transplantation was fueled by Dr. Blaiberg's book, *Looking at My heart*. Barnard would undertake an additional eight orthotopic heart transplants from 1967 to 1973, with the longest survivor living 23 years after transplant [5, 7].

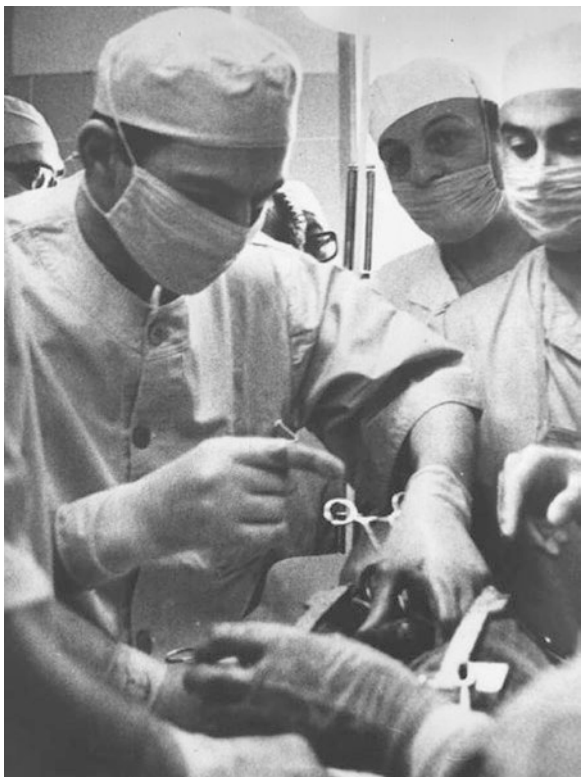

Fig. 25.8 World's first successful heart transplant. Christiaan N. Barnard, MD, performed the first human-to-human heart transplant on Dec. 3, 1967, at Groote Schuur Hospital in Cape Town, South Africa. Reprinted with permission from Central Press, Getty Images

Early Clinical Results for Human Cardiac Transplantation

Three days following the world's first successful heart transplant by Dr. Barnard, Adrian Kantrowitz, MD (Maimonides Medical Center, Brooklyn, NY), transplanted the heart of an anencephalic newborn into an 18-day-old infant with congenital heart disease [5, 7]. The recipient survived only 6.5 h after surgery.

By the late 1960s, more than 100 heart transplants had been performed. Due to dismal outcomes (mean survival of 29 days), a moratorium was placed on heart transplantation and only a few institutions continued to forge ahead. One of these institutions was Stanford University under the guidance of Dr. Shumway [5]. He and his team performed the fourth cardiac transplant on Jan. 6, 1968, with the recipient surviving 14 days (Fig. 25.10).

The 1-year survival of heart recipients improved to 65 % by 1978. Philip Caves, MD, developed a bioptome during this time that enabled endocardial biopsies to detect early organ rejection [5]. Research in rabbit antithymocyte globulin during this time also played a role in the treatment of rejection [12].

Fig. 25.9 The first successful heart transplants in the US Norman Shumway, MD, pioneered surgical techniques and performed one of the first successful heart transplants in the United States on Jan. 6, 1968, at Stanford Medical Center. Dr. Shumway is recognized as "the father of heart transplantation"

25

Table 25.1 History of Transplant Medicine

Date	Procedure	Physician(s)	Facility/location
1818	First successful blood transfusion	Dr. James Blundell	London, UK
12/23/1954	First successful renal transplant from living related kidney donor (identical twin)	Dr. Joseph E. Murray and Dr. David Hume	Brigham and Women's Hospital
04/05/1962	First successful renal transplant from deceased donor	Dr. Joseph E. Murray and Dr. David Hume	Brigham and Women's Hospital
03/01/1963	First successful human liver transplant	Dr. Thomas Starzl	University of Colorado Health Sciences Center
06/11/1963	First successful lung transplant	Dr. James Hardy	University of Mississippi Medical Center
12/17/1966	First successful pancreas/kidney transplant	Dr. Richard C. Lillehei and Dr. William Kelly	University of Minnesota
04/05/1967	First successful intestinal transplant	Dr. Richard C. Lillehei	University of Minnesota
12/03/1967	First successful human heart transplant	Dr. Christiaan Barnard	Groote Schuur Hospital (Cape Town, South Africa)
03/04/1968	First successful isolated pancreas transplant	Dr. Richard C. Lillehei	University of Minnesota
08/24/1968	First successful non-twin (allogeneic) bone marrow transplant	Dr. Robert A. Good	University of Minnesota
08/07/1968	Uniform Anatomical Gift Act established (Donor Card)		
10/30/1972	End-stage Renal Disease Program authorized by US Congress to promote Medicare coverage of renal dialysis and kidney transplant		
06/20/1979	First successful living related pancreas transplant	Dr. David E.R. Sutherland	University of Minnesota
03/09/1981	First successful heart-lung transplant	Dr. Bruce Reitz and Dr. Norman E. Shumway	Stanford Medical Center
11/1983	FDA Approval of CSA (Cyclosporin A)		
10/19/1984	National Organ Transplant Act (NOTA) establishes nationwide registry operated by UNOS, authorizes financial support for Organ Procurement Organizations (OPO), prohibits buying and selling of organs in the United States		
09/23/1998	First successful hand transplant	Dr. Earl Owen and Dr. Jean-Michel Dubernard	Lyon, France
11/27/2005	First successful partial face transplant	Dr. Bernard Devauchelle and Dr. Jean-Michel Dubernard	Amiens, France
03/20/2010	First successful full face transplant	Dr. Joan Pere Barret	Vall d'Hebron Hospital (Barcelona, Spain)

The research and continued operative success at Stanford showed promise for heart transplantation. Views on what constituted a donor remained in question [5]. Per Dr. Shumway [5]:

» *It should be underlined that no one can transplant a dead heart…Death of the donor is a diagnosis which must be made by the neurological and neurosurgical team.*

The donor pool was enhanced once the "Report of the Ad Hoc Committee of the Harvard Medical School to Examine the Definition of Brain Death" was released. This enabled greater acceptance of brain death criteria and was pivotal in promoting organ donation [5].

The FDA's approval of the use of cyclosporine in 1983 rekindled national interest in heart transplantation [12]. This "miracle drug" boosted the 5-year survival to 60 %. Cyclosporine was developed from a fungus, *Tolypocladium inflatum*, that was initially extracted from soil samples obtained by Jean-Francois Borel, MD (1933–), while vacationing in Norway [7, 12]. Dr. Borel was originally studying this fungus for antibiotic properties. In the early 1970s, the immunosuppressive properties of 24–556, the extract from *Tolypocladium inflatum*, were identified. Unlike other immunosuppressants at the time, 24–556 was more selective in inhibiting lymphocytes compared to depressing the entire immune system [7, 12]. The active metabolite from

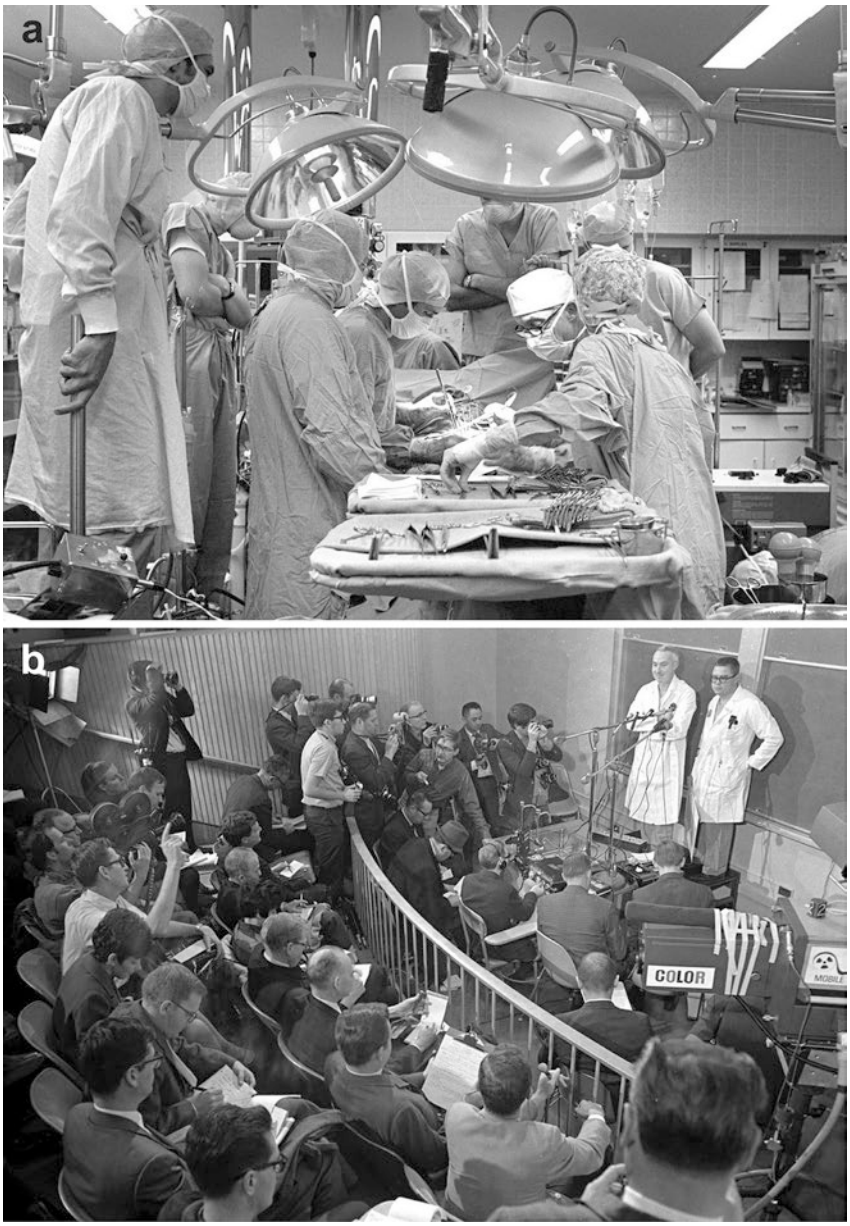

Fig. 25.10 The world's first successful heart-lung transplant. (**a**, **b**) Having implemented new immunotherapies, Drs. Reitz and Shumway performed the world's first heart-lung transplant in 1981 at Stanford University Medical Center

24 to 556 was purified and the compound CyA was discovered. This was eventually known as cyclosporin A.

Initially, due to the low interest in transplantation, the Pharmacology Department at Sandoz wanted to stop research on CyA unless Dr. Borel could offer more clinical proof of his discovery [12]. In 1976, Dr. Borel presented his findings at the British Society of Immunology. Two surgeons, Sir Roy Calne, MD, and David White, MD, approached Dr. Borel for samples of CyA. They used those samples in heart-transplanted mice. High doses were given and hepatic and nephrotoxicity ensued. Dog trials were undertaken but failed. Failure was later determined to be caused by low absorption.

Human trials were started but halted when it was found that the drug was not being absorbed. The preparation at this time consisted of pure cyclosporine in gelatin tablets. In 1977, three of the researchers—Dr. Borel; Hartmann Stähelin, MD; and B. von Graffen, MD—tested new preparations of the drug on themselves after determining proper laboratory tests that could accurately measure the serum drug levels [12]. The preparation found to have the most efficacy was an oral solution containing ethanol and detergent.

The next year, human trials led by Sir Roy Calne resumed on kidney transplant patients. Initial results were troubling as many patients developed hepatotoxicity, nephrotoxicity, and lymphoma. Through several more human trials using decreased dosage and the addition of steroids, morbidity from cyclosporine A was lowered to an acceptable level. The drug was approved for use in the United States 5 years later.

Cyclosporin A was later used and contributed to the success of the first heart-lung transplant performed by Bruce Reitz, MD, and Dr. Shumway (Fig. 25.11 and Table 25.1). An uncommon persistence, vision, and research depth separated Dr. Shumway and his team from the rest of the world of transplant clinicians. Shumway would oversee about 800 cardiac transplants from 1968 to 1993, coauthor more than 500 publications,

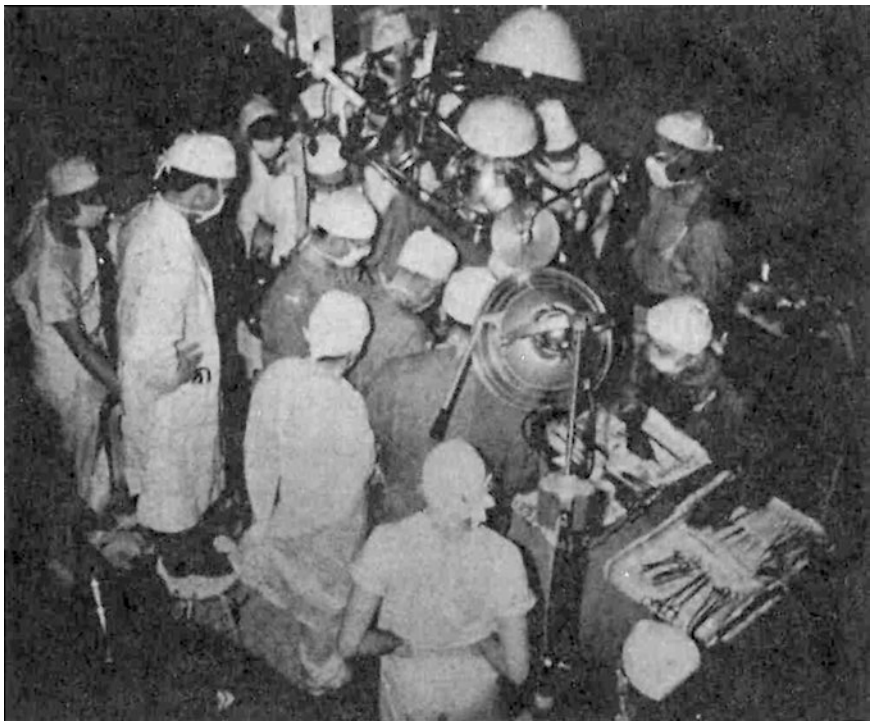

Fig. 25.11 World's first successful open heart surgical procedure. Using hypothermia, the world's first successful open-heart surgical procedure was performed on Sept. 2, 1952, at the University of Minnesota Medical Center. F. John Lewis, MD, was assisted by Dr. Richard Varco and Dr. C. Walton Lillehei, and used hypothermia to cool the five-year-old child's body to 28oC and close the atrial septal defect. *Source*: Unknown

and train scores of surgeons who, in turn, led cardiovascular surgical programs across the world. Today, Dr. Shumway is widely regarded as the "father of heart transplantation" [11].

Triple Drug Immunotherapy

The goal of immunosuppression is to (1) sufficiently suppress the recipient immune system to avoid damage to the transplanted organ, (2) not completely suppress the recipient so as to enable adequate response against infection, and (3) provide a complementary combination of medications that optimize immunosuppression while decreasing toxicity [12]. Early immunosuppression therapy consisted of radiation (1950s), azathioprine and/or corticosteroids (1960s), and antilymphocyte globulin/antithymocyte globulin (1960s–1970s).

The following section describes the development of the third goal of immunosuppressive therapy.

As previously stated, cyclosporin A revolutionized immunosuppression in organ transplantation. Secondary to toxicity, different drug combinations were introduced. Initially, cyclosporin A was used as monotherapy; however, because of nephrotoxicity, corticosteroids were added to the regimen. This allowed for lower dosing of cyclosporin A, decreases in nephrotoxicity, and improved graft survival. This regimen was further fine-tuned with the addition of azathioprine [12].

Azathioprine and corticosteroids were the mainstay immunosuppression therapy before the introduction of cyclosporin A. Azathioprine selectively downregulates T cell activity and suppresses cell-mediated rejection. In 1959, mercaptopurine (6-MP) was shown to suppress humoral immunity. Soon after this discovery, Sir Roy Calne determined prolonged renal graft survival in dogs with the use of 6-mercaptopurine (6-MP) [12, 13]. Azathioprine is 6-MP with an additional side chain, which provides a less toxic form of 6-MP.

Corticosteroids were introduced in renal transplantation in 1963 [12]. Steroids' main mechanism of action is lymphocyte depletion, mostly in T cells. B cell activity is not susceptible to steroids. Steroids clearly have many side effects, including hypertension, obesity, hyperglycemia, and osteoporosis. Theoretically, triple drug therapy enables lower doses of each of these drugs, thus maintaining efficacy while decreasing the toxic effects. The 1990s introduced another metabolite, mycophenolate mofetil, and the calcineurin inhibitor, tacrolimus, which are also used in triple drug regimens today [13].

A Recipe for Innovation and Discovery: The University of Minnesota

The innovations and discoveries that mark the field of heart transplantation, immunotherapies, and device support were only possible through the emphasis on research. The adage, "every failure brings success one step closer," underscores the importance of learning from every failed experiment. This philosophy requires a culture that emphasizes the essential role of research in clinical medicine. While the success of heart transplantation received worldwide attention, this accomplishment was only possible from decades of research.

Success does not emerge from a vacuum, but is built on the shoulders of many pioneering initiatives. Historically, one might ask why an inordinate number of cardiovascular surgical discoveries emerged from one program at one

Fig. 25.12 Surgical pioneer revolutionized cardiovascular medicine. Dr. C. Walton Lillehei, regarded as the "father of open heart surgery," impacted the field with surgical innovations and by training hundreds of surgeons across the world

institution. The short answer is leadership—institutional leadership that understands and values research and innovation. Leadership attracts faculty members and inspires them to take bold but calculated risks with their research—encouraging them to address big questions for their field (Table 25.1).

One such leader was Owen H. Wangensteen, MD, PhD [11, 14]. Dr. Wangensteen transformed the University of Minnesota Surgical Department and emphasized the essential role of basic science research and clinical medicine (Fig. 25.6). As department chair, Dr. Wangensteen required every faculty member to have a research laboratory and to pursue collaborative interactions with basic scientists [11]. He established a culture of intellectual risk taking, innovation, and discovery. For example, this culture yielded a number of "firsts," including Dr. Lewis performing the world's first successful open heart surgical procedure using hypothermia on Sept. 2, 1952 (Fig. 25.12) [11].

These innovations and bold initiatives were not only encouraged but they were demanded. Faculty members' rigor and creativity served as magnets for the recruitment of faculty and trainees alike. Dr. Wangensteen further required that all surgical trainees pursue PhD research training. Collectively, this culture and program produced an unprecedented array of trainees who would become academic leaders, discoverers, and industry leaders who would have a profound and lasting impact on clinical medicine [11]. These innovations and discoveries fueled visibility, reputation, and impact on the field and, ultimately, the lives of patients.

One of the emerging leaders at the University of Minnesota was Dr. Lillehei, "the father of open heart surgery" (Fig. 25.1) [11, 15]. Without his pioneering studies, cardiac surgery, let alone heart transplantation, would not have been possible (Fig. 25.13) [11, 15]. In 1954, Dr. Lillehei and associates performed a repair of a ventricular septal defect in a young boy using cross-circulation and the boy's father as the biological oxygenator (Fig. 25.14) [11]. Flow from the patient's cava was routed to the father's femoral vein, oxygenated, and returned to the patient via the carotid artery. This proved to be a major advance in cardiac surgery, although not widely used secondary to the risk to the parent. Through the continued research of Drs. Lillehei and Richard DeWall, the first effective bubble oxygenator was engineered and developed (Fig. 25.5) [11]. For 20 years, their invention was the standard for extracorporeal circulation.

The first heart transplant at the University of Minnesota Medical Center was performed in 1978 by Demetre Nicoloff, MD (August 2003), and William Lindsay, MD [14]. Although the first transplant in the world was performed in South Africa in 1967, Dr. Barnard trained under Dr. Wangensteen (Sept. 21, 1898–January 1981), Dr. Lewis, and Dr. Lillehei [11]. Newer immunosuppression medications were becoming available during this time and allowed for the first successful heart-lung transplant in 1986 at the university [14]. In 1987, the first heart-kidney transplant in the state of Minnesota was performed at the university. University of Minnesota physicians also performed the heart transplant on one of the longest-surviving recipients. As this text went to press, she continues to survive and lead a productive life more than 35 years after her heart transplant.

Mechanical Circulatory Support

Soon after the first use of the cardiopulmonary bypass machine, other uses for this technology became apparent with support for patients in postcardiotomy cardiogenic shock. The 1960s brought with it rudimentary cardiac assist devices to use in postoperative patients with shock. The initial use of an implantable cardiac assist device occurred in 1963 by Liotta [16]. This first design of an assist device consisted of a tubular displacement pump that was pneumatically driven. The device was connected to the left atrium and descending thoracic aorta. The left ventricular assist device supported the patient for 4 days, after which the patient died from multi-organ system failure. Although the patient did not survive, initial results were encouraging and, in 1964, the National Institutes of Health created the Artificial Heart Program [16].

In 1966, Michael Debakey, MD, used a pneumatic left ventricular device on a patient with postcardiotomy shock. After 10 days of support, the patient survived. With the first heart transplant performed in 1967, this new technology was explored as a bridge for patients until they could be transplanted. In 1969, Dr. Cooley used the first total artificial heart as a bridge to transplant [16]. While the early 1970s saw a moratorium on transplants due to poor outcomes and inadequate immunosuppression, this served as an inspiration to fine-tune mechanical support devices. The pneumatic devices available at this time could only support patients for a few days, caused significant hemolysis and thrombosis, and were cost-prohibitive.

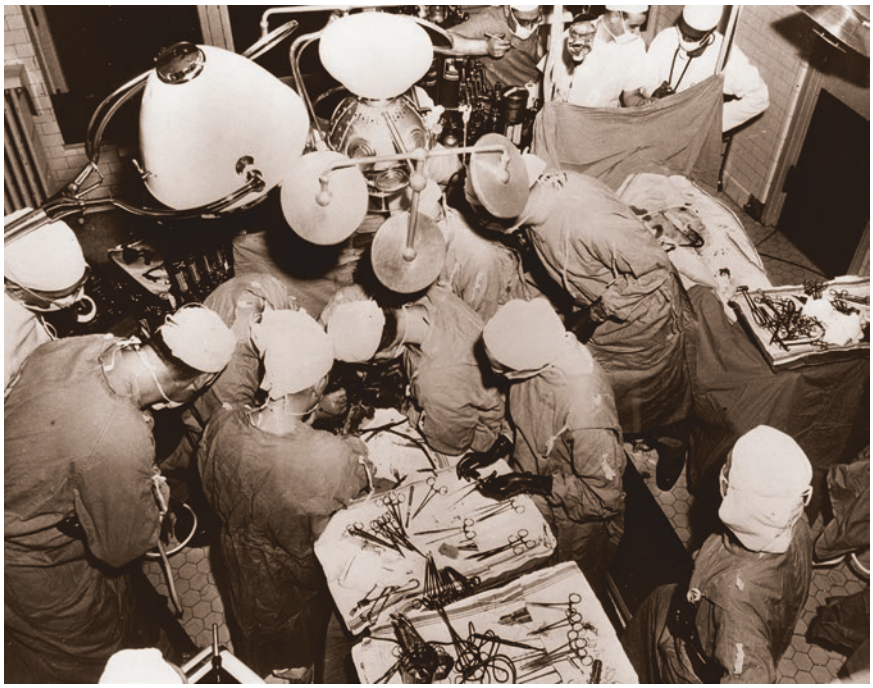

Fig. 25.13 Cross-circulation provided a platform that launched cardiac surgical procedures. Dr. C. Walton Lillehei used cross-circulation on March 26, 1954, to surgically repair a ventricular septal defect. Drs. C. Walton Lillehei, Richard Varco, Herbert Warden, and Morley Cohen received the Lasker Award in 1955 for cross-circulation and advances in cardiac surgery

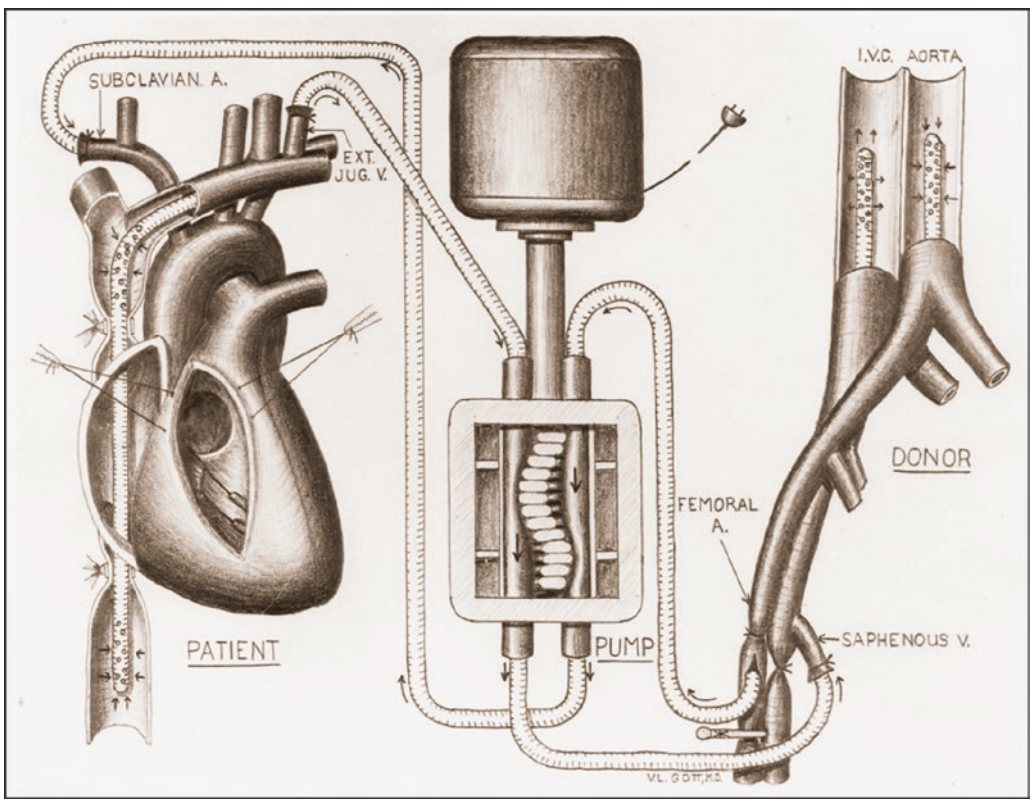

Fig. 25.14 Schematic representation of the cross-circulation procedure. Typically, children with congenital heart disease (patients) would have their blood pumped to an ABO-compatible relative (usually a parent) who would serve as the biological oxygenator. Between 1954 and 1955, 45 patients were supported using cross-circulation for their surgical procedure at the University of Minnesota Medical Center. When an ABO-compatible relative was unavailable, dog lungs were successfully used as the biological oxygenator in more than five patients at the University of Minnesota Medical Center

During this time, Novacor was refining the design of its ventricular assist device to make it more reliable and compact and to increase its efficiency [17]. Barney Clark, MD, became the recipient of the Jarvik-7 in 1982—a total artificial heart. He survived 112 days but eventually succumbed to infection. Total artificial heart development halted for a few years because of the high rates of complications: infection, stroke, and thrombosis.

In 1982, with persistence and ingenuity, Novacor developed a pulsatile left ventricular assist device to use as a bridge to transplant. It was first implanted in 1984 [17]. The patient's condition improved after implantation, and 9 days later, the patient successfully underwent a heart transplant. The FDA then approved multiple pulsatile devices in the mid-1990s; with fewer than 4000 donor hearts available, the devices were much needed.

In 2003, the FDA approved the Heartmate XVE for destination therapy. This supported treatment strategies for patients ineligible for transplant. Since then, many other assist devices have become available such as the Heartmate II (Thoratec), Heartmate III (Thoratec), CardioWest TAH-1 (Syncardia), and the Heartware. Survival at 1 year has been >80 % with current FDA-approved devices and the technology continues to improve.

Summary

The road to heart transplantation was an exercise in endurance and perseverance by many gifted individuals. From the basic building blocks of vascular anastomosis to the advent of cardiopulmonary bypass and the monumental discovery of cyclosporin A, all of these breakthroughs led to modern-day heart transplantation. Future improvements in treatments for heart failure and subsequent heart transplants will rely on improving mechanical circulatory devices, immunosuppression regimens, and ways to increase donor availability.

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