MAJOR MEDICAL MILESTONES LEADING UP TO THE FIRST HUMAN HEART TRANSPLANTATION

KATE ELZINGA

SUMMARY: Throughout the historiography of cardiac surgery, it was claimed that the first heart operation was performed in 1801 by Catalonian physician Francisco Romero (ca. 1770-1815?). His pericardiostomy involved making a thoracic incision, then opening and draining the pericardium. "Blood oxygenation" did not restrict this type of minor surgery, but proved to be a significant barrier limiting cardiac surgery for the next 150 years. Open heart surgery only became possible with the creation of the cardiopulmonary bypass machine and the use of medically induced hypothermia. Dr. Wilfred Bigelow (1913-2005) discovered that if dogs were cooled to 25-30°C, they could be brought back to consciousness in warm water, which was very encouraging because heart operations would be safer if a patient's oxygen demands were decreased during surgery. This article will address some not-so-well known Canadian achievements leading up to the development of cardiac surgery in general and heart transplantation in particular and put them into their perspective in the wider history of medicine.

KEYWORDS: History of Heart Surgery, Cardiac Surgical Procedures, Heart Transplantation, Induced Hypothermia, Animal Experimentation, Francisco Romero, Wilfred Bigelow, Christian Barnaard.

PRECEPTOR: Dr. Paul Fedak ■ INSTITUTION: University of Calgary

Introduction

"Where there is death, there is hope." This was the slogan displayed on the wall of Dr. Norm Shumway's (1923-2006) office in Palo Alto, California, revealing his desire to use donated hearts to save patients with terminal heart failure to prevent a dismal prognosis. Known as "the father

of cardiac surgery,"[1] Shumway established the technique of heart transplantation. However, he was beaten in the race to perform the first human heart transplant by a South African cardiac surgeon Christian Barnard (1922-2001). This monumental feat was performed on December 3, 1967, by Barnard in Cape Town, South Africa. The success of human heart transplantation was not due to the efforts of Shumway and Barnard alone, but culminated from the work of surgeons and scientists from around the world. As Barnard stated shortly after the surgery:

> The achievement did not come as a surprise to the medical world. Steady progress towards this goal has been made by immunologists, biochemists, surgeons, and specialists in other branches of medical science all over the world during the past decade to ensure that this, the ultimate in cardiac surgery, would be a success.[2]

As the ability to transplant other organs became a reality, the possibility of heart transplantation became more feasible. Years of research were dedicated to the development of the complex technical surgical skills necessary to perform human heart transplantation. In addition, there were important medical milestones that became critical to the success of heart transplantation. These milestones included ABO blood type matching, the discovery of immunosuppressive and antibiotic medications, and the advent of cross-circulation, medical hypothermia, as well as the invention of cardiopulmonary bypass machine. Through the review of historical and current medical journal and newspaper articles, textbooks, and novels, these essential medical advances will be described and their vital role in the success of cardiac transplantation revealed.

The Beginnings of Human Solid Organ Transplantations

The kidney was the first organ to be successfully transplanted. The kidney is a paired organ, yet humans only require one for survival, making it a highly suitable organ for transplantation. In fact, one in 11,000 people are born with only one kidney.[3] Most of these individuals never discover the fact that they have a single kidney because they are asymptomatic

---

[1] Caroline Richmond, "Norman Shumway," *British Medical Journal* 332 (2006), p. 553.

[2] Sat Sharma and Helmut Unruh, *History of Adult Transplantation. 2006*; retrieved 1 February 2008 (http://emedicine.medscape.com/article/430267-overview).

[3] Ronald Munson, *Raising the Dead: Organ Transplants, Ethics, and Society* (New York: Oxford University Press, 2002), p. 101.

throughout their life. The kidney is also a favourable organ for transplantation because its blood flow is relatively simple, and it is therefore technically less difficult to transplant kidneys as compared to other organs such as the heart, lungs, liver, and pancreas.

The first successful organ transplantation was performed between genetically identical twins. Organ transplantation between monozygotic twins offers a greater chance of success, because there is a lower likelihood of immune rejection between monozygotic twins than between dizygotic twins, family members, and genetically-unrelated recipients and donors. In the years prior to the first organ transplantation, it had been determined that skin grafts donated from family members survived longer than those from unrelated donors. This was due to similarities in antigenicity between genetically related donors and recipients. In 1937, Dr. James Barrett Brown (1899-1971) was able to achieve permanent survival of skin grafts between monozygotic twins.[4] Dr. Joseph Murray (b. 1919) made use of these ideas and on December 23, 1954, he became the first surgeon to successfully perform both a human organ transplant and a kidney transplant between a set of identical twins, the Herrick brothers. The twins were 23 years old at the time of the transplant which was performed at the Peter Bent Brigham Hospital in Boston.[5] The recipient, Richard Herrick (1931-1962), had been suffering from severe kidney disease, which had begun two years earlier. Initially he had been troubled by peripheral oedema, hypertension, hematuria, and proteinurea, and then progressed to develop pulmonary oedema and cardiomegaly. These signs and symptoms were due to his severe renal failure that had likely developed as a sequela to the scarlet fever he had suffered as a child. Unfortunately, dietary restriction and medications were not sufficient to reverse or stop the progression of his kidney failure. By donating one of his kidneys to his brother, Ronald Herrick (1931-2010) subsequently saved Richard's life.[6] Richard survived for eight years after the transplantation with his new kidney.

Murray was awarded the Nobel Prize in Physiology or Medicine in 1990 along with Dr. E. Donall Thomas (b. 1920) for their advances in organ and cell transplantation in the treatment of human disease. Murray's success in renal transplantation was followed by the successful

---

[4] John B. Brown, "Homografting of Skin: With Report of Success in Identical Twins," *Surgery* 1 (1937), pp. 558-563.

[5] M. Wayne Flye, *Principles of Organ Transplantation* (Philadelphia: W.B. Saunders Company, 1989), p. 126

[6] David Petechuk, *Organ Transplantation*. 3rd ed. (Westport, Conn.: Greenwood Press, 2006), pp. 234-232.

transplantation of the pancreas in 1966, of the liver in 1967, and of the heart in 1967. Organ transplantation became viewed as a major medical milestone because it could now save the lives of patients who had failed all other available medical and surgical therapy. The successful transplantation of the kidney also paved the way for the transplantation of other organs. Important lessons were learned from both the successes of earlier kidney transplantation and from the difficulties kidney transplantation surgeons had faced. The techniques used in kidney transplantation and the observations of immune rejection in these transplants gave cardiac surgeons valuable insight which contributed to the success of heart transplantation. The first human heart was successfully transplanted thirteen years after the first kidney transplant, thus demonstrating the rapid progression of transplant surgery.

Heart Transplantation: The Development of the Required Technical Surgical Skills

The first heart surgery was successfully performed in 1801 by Francisco Romero (1700-1763), a Spanish surgeon. He performed an open pericardiostomy to treat a pericardial effusion.[7] This involved making a thoracic incision, then opening and draining the pericardium.[8] Over the years since this relatively straightforward operation was performed, cardiac surgeons have made great progress in their surgical techniques and have developed sophisticated methods to repair severe heart defects due to both congenital and acquired causes.

For more than a century and a half after the first heart surgery was performed; Dr. Richard Lower (1930-2000) began to explore the idea of heart transplantation. Lower worked closely with Shumway at the Stanford School of Medicine for years in the field of cardiac surgery, while Shumway regarded Lower as the best experimental researcher he had ever known.[9] During reparative surgery of heart defects in dogs in the laboratory, Lower began to consider the possibility of replanting a donor heart, allowing any defects to be removed along with the recipient's heart and be replaced by a healthy organ. Through their meticulous research

---

[7] Alejandro Aris,"Francisco Romero, The First Heart Surgeon," *The Annals of Thoracic Surgery* 64 (1997), pp. 870-871.

[8] Harold Robert Shumacher, Jr., "When Did Cardiac Surgery Begin?," *Journal of Cardiovascular Surgery (Torino)* 30 (1989), pp. 246-249.

[9] Donald McRae, *Every Second Counts: The Race to Transplant the First Human Heart* (New York: Penguin Group 2006), p. 69.

and the extensive use of animal models, Lower and Shumway revolutionized the field of cardiac surgery.

In 1959, Lower performed his first heart transplantation: an auto transplantation in a dog. The short and fragile aortas of dogs made the auto transplantations very difficult. Lower soon hypothesized that it would be more practical to transplant a heart from one dog to another as this would preserve more tissue, allowing him to join the tissues and blood vessels of the transplanted heart to the recipient's body more easily and more effectively. Along with Shumway, Lower performed their first successful heart transplant on December 23, 1959, at the Stanford Hospital Centre in Palo Alto, California. The recipient dog did very well until signs of rejection became evident eight days after the transplant. Although the dog could have survived for up to another week, the surgeons decided to euthanize the dog to examine its heart before the tissue was completely degraded. During post-mortem examination, the transplanted heart was found to be normal and healthy.

Lower and Shumway acknowledged the possibility of organ rejection, but they were on their way to perfecting the surgical techniques required to perform the procedure. Lower became increasingly proficient in transplantation, eventually performing over 300 heart transplants in dogs. He learned how to keep the recipient alive using a cardiopulmonary bypass machine, how to prevent blood clots, how to stitch in the new heart using anastomoses to the atria, pulmonary artery, and aorta, and how to store a donor organ in icy saline until the organ was ready to be put into the recipient's chest. Lower became the chief of cardiac surgery at the Medical College of Virginia in Richmond, Virginia, after Shumway recommended him to the hospital's chief of surgery who wanted to establish a program in heart transplantation. While attending a course on transplantation organ rejection with American surgeon Dr. David Hume (1917-1973) in Richmond from August to October 1966, Barnaard observed Lower perform numerous heart transplants in dogs. He scrutinized Lower's efficient and precise surgical technique, absorbing every detail of the procedure. Fascinated by the prospect of becoming the first to carry out heart transplantation in a human being, Barnaard resolved to perform the same surgery when he returned home to Cape Town, South Africa. Despite Lower and Shumway's impressive eight years of preparation in heart transplantation and his own considerable lack of laboratory research, Barnaard was determined to beat Lower and Shumway in the race to perform the first human heart transplant.

By November 1967, Lower and Shumway had performed over 300 heart transplants in dogs, Dr. Adrian Kantrowitz (1918-2008), another

prominent American cardiac surgeon and researcher, had completed 270, and Barnard's Cape Town team had only performed 48 at that time. However, the surgeons already felt confident that they had mastered the technique and were ready to perform the transplants on humans.

Organ Compatibility: The Discovery of ABO Blood Types

ABO blood type matching was first discovered between 1900 and 1901 by Dr. Karl Landsteiner (1868-1943) at the University of Vienna. Landsteiner went on to win the Nobel Prize in Physiology or Medicine in 1930 for discovering and creating the modern system of blood classification. He had observed that in certain blood transfusions, the recipient developed jaundice, haemoglobinuria, and went into shock. To investigate this phenomenon further, he first tested the blood of his colleagues and discovered that serum from some individuals could cause agglutination or haemolysis of the red blood cells of certain other individuals while having no effect on the red blood cells of others. Through his experiments, he concluded that there were three different blood types. Landsteiner named the types A, B, and C, which are known today as A, B, and O. In 1902, his colleagues Alfred von Decastello (1872-1960) and Adriano Sturli (1873–1964) discovered the fourth and final blood type, AB.

In 1910, Landsteiner made the discovery that blood types are actually inherited. Thirty years later in 1940, with Alexander Weiner (1907-1976), he discovered the Rh blood group. Throughout his career, he investigated other blood types and coined the term "hapten" for small molecules which elicit an immune response only when they are attached to a larger carrier molecule. Landsteiner's work in serology, immunochemistry, and immunology were fundamental in allowing blood and organ transplantation to be successful.[10] A few years earlier, in 1907, Dr. Ludwig Hektoen (1863-1951), the head of the pathology department at the University of Chicago, recommended that all blood donors and recipients be cross matched prior to transfusion. By the time of World War One had begun, blood typing was a common practice and was well understood and accepted by the medical community. The risk of a transfusion reaction from a properly matched donation was virtually eliminated.

In October 1966, Lower had the opportunity to perform the first human heart transplantation, for he had a donor and a recipient prepared for the

[10] Albert E. Chudley, "Genetic Landmarks Through Philately: Karl Landsteiner: The Father of Blood Grouping," *Clinical Genetics* 57 (2000), pp. 267-269.

transplant and his staff was ready to perform the operation; however Lower refused to proceed due to an ABO blood type incompatibility between the donor and the recipient. Although a full recovery is possible after an ABO-incompatible transfusion, death can also result. Despite the protests of his colleagues urging him to become the first physician to perform a human heart transplant, Lower was vigilant and correct in refusing to transplant an ABO incompatible organ.

Prevention of Organ Rejection: The Discovery of Immunosuppressive Drugs

With the advent of organ transplantation, the need for immunosuppressive drugs became rapidly apparent. Physicians observed how the recipient's immune system rapidly mounted a response against the transplanted organ they received. Evidence of graft rejection dates that were performed back as early as 1661 when the rejection of a skin graft on a patient's nose was documented in Sir Kenelm Digby's (1603-1665) book *Eroeffnung unterschiedlicher Heimlichkeiten der Natur*.[11] Cardiac transplantation was not exempt from the challenges of organ rejection. In fact, during his presentation at the Sixth International Transplantation Conference on February 8, 1964, Shumway presented four areas of particular difficulty his group had faced: preservation of the heart, post-transplant circulatory support, early detection of rejection, and case selection. The outcomes of organ transplantation without immunosuppressive therapy, however, were still very poor.

The use of adrenal steroids and whole body irradiation in the 1950s began to prolong kidney transplant survival by weakening the recipient's immune system.[12] Prednisone, a corticosteroid still commonly used today, was discovered in 1951 by Arthur Nobile (1920-2004).[13] Prognosis after transplantation continued to improve after the discovery of 6-mercaptopurine in 1951 and a 6-mercaptopurine derivative, azathioprine, shortly after, by Dr. Gertrude Elion (1918-1999) and Dr.

---

[11] David Hamilton and James T. Goodrich, "An Illustration of Skin Graft Rejection and Sympathetic Medicine from 1661," *Bulletin for the History of Medicine* 60 (1986), pp. 217-221.

[12] Philip F. Halloran and Sita Gourishankar, "Historical overview of pharmacology and immunosuppression". In: *Primer on Transplantation*, eds. Douglas J. Norman, Laurence A. Turka. 2nd ed. (Manchester: Blackwell Publishing 2001), pp. 71-75.

[13] Arthur Nobile, *Steroids* 59 (1994), pp. 227-230.

George Hitchings (1905-1998).[14] Dr. Roy Calne (b. 1930), a surgeon working at Saint Mary's Hospital in London, England, was successful in delaying kidney rejection in dogs for forty-four days with the use of 6-mercaptopurine, increasing survival time from the usual rejection time of ten days.[15] Also, the survival time was further increased with the use of azathioprine.

In 1967, Shumway was optimistic and was quoted saying, "We think that the way is clear for a trial of human heart transplantation"[16] after the recent use of antilymphocyte globulin had significantly increased the long-term survival rate in kidney transplants. Azathioprine and prednisone was the mainstay of immunosuppressant therapy used in transplantation medicine until the discovery of cyclosporine in 1978. Cyclosporine was the first sufficiently powerful immunosuppressive medication that allowed transplants to become life-saving treatments, rather than experimental research.

The use of immunosuppressants reduced the likelihood of rejection of the foreign organ by the heart transplant recipient's immune system during the first human heart transplantation in 1967. However, the immune system was not yet well understood and the mechanism of rejection needed further investigation. For example, T- and B-lymphocyte subsets were not defined until 1968 and the introduction of MHC (major histocompatibility antibodies) was still restricted, because the nature of the adaptive immune response was not understood until 1974. The world's first heart transplant recipient, Louis Washkansky (1913-1967), began to develop a growing lung shadow as shown on his chest X-rays on December 16, 1967, thirteen days after he received his transplanted heart: "It looked like the classical onset of pneumonia but Barnard was more unsettled by the mysteries of rejection". Over the next few days, Washkansky's temperature rose, he had difficulty breathing, he complained of chest pain, and his peripheral circulation began to decrease. As a consequence from these clinical observations, Barnaard altered the doses of Washkansky's immunosuppressive medications, erratically changing the amount of actinomycin, azathioprine, hydrocortisone, and prednisone Washkansky was receiving. Barnard was not prepared to detect the early signs of rejection and could only guess what was going on

---

[14] Gertrude B. Elion, "The Quest for a Cure," *Annual Review of Pharmacology and Toxicology* 33 (1993), pp. 1-23.

[15] Roy Yorke Calne, "Inhibition of the Rejection of Renal Homografts in Dogs by Purine Analogues," *Transplantation Bulletin* 28 (1961), pp. 65-81.

[16] Adrian Kantrowitz, "America's First Human Heart Transplantation: The Concept, the Planning, and the Furor," *ASAIO Journal* 44 (1998), pp. 244-252.

in Washkansky's body. Unsure of the diagnosis, Barnard also prescribed penicillin to fight a possible bacterial pneumonia and used anti-coagulation medications to prevent a pulmonary embolism.

On December 21, 1967, after surviving eighteen days with his new heart, Washkansky succumbed to his infection. His anti-rejection therapy had been successful in preventing organ rejection, but at the same time it had depleted his immune system so effectively that he had developed bacterial growths of klebsiella and pseudomonas in his lungs. In his frantic battle to fight rejection, Barnard had overlooked the simple diagnosis of pneumonia which had ultimately killed his patient. During the autopsy, the pathologist found a healthy heart that showed no signs of rejection and confirmed that pneumonia had been the cause of death.

The Discovery of Antibiotics: The Prevention of Post-Operative Infections

With the discovery and use of immunosuppressive therapies, the risk of infection and the number of infections caused by unusual organisms increased dramatically. This was evident in Washkansky's case of pneumonia. In a normal host, klebsiella and pseudomonas are uncommon causes of pneumonia, but in the immunosuppressed, these bacteria can invade at a considerably higher rate. By suppressing the transplant recipient's immune system and host defences, bacteria, viruses, fungi, and other organisms are more capable of causing infection. As immunosuppression becomes more potent, the risk of infection rises. Today, the guidelines for patients undergoing cardiac surgery recommend antibiotic prophylaxis to prevent infections because infections can lead to serious complications and increased morbidity and mortality.[17]

Joseph Lister (1827-1912), an English surgeon working at the Glasgow Royal Infirmary in Scotland, was the first surgeon to prevent post-operative infections through the use of antiseptics. His use of carbolic acid as an antiseptic stemmed from the observations of the effectiveness of carbolic acid in killing the parasite entozoan.[18] Using carbolic acid, he was able to reduce the number of infections acquired by his patients after surgery. The implementation of aseptic techniques greatly reduced the

[17] Society of Thoracic Surgeons Workforce on Evidence Based Surgery, *Antibiotic Prophylaxis in Cardiac Surgery. Part 1, Duration of Prophylaxis* (Chicago: Society of Thoracic Surgeons, 2005), p. 20.

[18] David Guthrie, *Lord Lister* (Edinburgh, Scotland: Livingston LTD, 1949), pp. 156- 157.

incidence of infection and thus resulted in better surgical outcomes. Limbs that would previously have been lost to infection could be saved with the use of carbolic acid. Lister also discovered that a diluted solution of 1:20 carbolic acid to water was very effective in killing microorganisms that caused infections while being less irritating to wounds than pure carbolic acid. He further reduced the risk of sepsis by the use of heat to sterilize surgical instruments.[19] He would also sterilize his instruments, as well as his hands, during his procedures using carbolic acid. Moreover, Lister dipped his catgut sutures into carbolic acid before using them to stitch up patients. The sutures could then be safely left in and absorbed by the patient's body because the risk of infection was reduced.

Louis Pasteur (1822-1895), a French chemist and microbiologist, was able to prove that infection was caused by bacteria and disproved the idea of spontaneous bacterial generation.[20] Lister believed in the work of Pasteur, a fellow innovator of the period, and it had been Pasteur's discovery of atmospheric germs that prompted Lister to utilize techniques to decrease the chances of these germs causing infections in his patients.[21] While the implementation of aseptic technique was a major step in the prevention of post-operative infections, it did not eradicate infections all together. Despite the use of carbonic acid, heat and improved sterile handling techniques, infections continued to plague patients after surgery. To combat these infections, antibiotics had been developed and increasingly used. Penicillin was the first substance to be recognized as an antibiotic. The discovery of penicillin was made in 1928 by Alexander Fleming (1881-1955), a Scottish bacteriologist at the University College London in England. Fleming has observed the effects of the mold Penicillium on a staphylococcal bacterial culture and this led to the development of penicillin as an antibiotic.

The efficacy of penicillin was established during World War Two. Prior to World War Two, penicillin had not been mass produced and this severely limited its availability for use. The demand for an antibiotic to fight gram-positive bacteria was amplified during World War Two and major efforts were made to increase the production of penicillin. On March 14, 1942, penicillin was used to treat a β-haemolytic streptococcal septicaemia in a patient at Yale-New Haven Hospital in Connecticut, thus

---

[19] Nikorn R. Arunakul, "Dr. Joseph Lister: The Founder of Antiseptic Surgery," *Primary Care Update for OB/GYNS* 10 (2003), pp. 71-72.
[20] Donald S. Burke, "Louis Pasteur," *Journal of the American Medical Association* 283 (2000), pp. 2587-2588.
[21] [Ludwig] Haas, "Louis Pasteur (1822-95)," *Journal of Neurology, Neurosurgery and Psychiatry* 66 (1998), pp. 685-688.

marking penicillin's first clinical use in the United States.[22] Alexander Fleming, Sir Howard Florey (1898-1968), and Dr. Ernst Chain (1906-1979) were awarded the Nobel Prize in Physiology or Medicine in 1945 for the discovery of penicillin and its curative effect in various infectious diseases. Antibiotics greatly decreased the number of patient deaths due to infection. The efficacy of antibiotic medications was conclusive and the clinical use of antibiotics was widespread. Antibiotics were used in many fields of medicine, including that of cardiac surgery. For instance, after performing the first human heart transplant, Barnaard treated the recipient with antibiotics post-operatively because he suspected a possible pneumonia growing in his patient's lungs. Antibiotics also played a role in the post-operative care of subsequent heart transplant recipients and may have contributed to the long term survival of many of these patients. Without the discovery of antibiotic therapy, there is little doubt that post-operative infection rates would have increased significantly and the prognosis of patients would be diminished.

Creating a Dry Field: The Use of Hypothermia and the Discovery of the Cardiopulmonary Bypass Machine

The development of the cardiopulmonary bypass machine was essential to the field of open heart surgery and heart transplantation. Open heart surgery become possible with the invention of the cardiopulmonary bypass machine in 1951 and the use of hypothermia in 1952 which allowed a bloodless and motionless field to be created. Dr. Wilfred Bigelow (1913-2005), a Canadian surgeon, was the first to experiment with the use of hypothermia in a medical setting after he considered the limitations of closed heart surgery. He stated in 1947,

> I became aware that surgeons obviously would never be able to correct or cure [many] heart conditions unless they were able to stop the circulation of the blood through the heart, open it, and operate in a bloodless field under direct vision.[23]

Intrigued by the phenomenon of hibernation in groundhogs, Bigelow was inspired to investigate the use of hypothermia medically, undertaking

---

[22] Grossman, Charles M, "The First Use of Penicillin in the United States," *Annals of Internal Medicine* 149 (2008), pp. 135-136.

[23] Wilfred Bigelow (1947), qtd. after Will C. Sealy, "Hypothermia: It's Possible Role in Cardiac Suergery," *Annals of Thoracic Surgery* 47 (1989), pp. 788-791; here: p. 788.

hypothermia research using dogs. Dogs have a normal body temperature between 37.8-39.2 degrees Centigrade.[24] Through his experiments, Bigelow discovered that if the body temperature of the animals was reduced below twenty degrees Centigrade, the dogs could no longer be brought back to consciousness. But when the dogs were cooled to twenty to twenty-five degrees Centigrade, they could be brought back to consciousness in warm water without any mental or physical deterioration after surgery. These were encouraging results because by reducing a patient's body temperature prior to an operation and thus decreasing their oxygen demands, heart operations could be made much safer.

The first human open heart surgery using hypothermia was performed by Dr. John Lewis (1916-1993) on September 2, 1952, at the University of Minnesota.[25] The patient's body was cooled to twenty-eight degrees Centigrade using an ice-packed tank and cooling blankets. Once the patient's heart rate had decreased to half of its normal rate, the patient's chest was opened and the heart was exposed. An atrial septal defect was successfully repaired. The patient's chest was then closed and the patient's normal body temperature was restored through the use of a tub of warm water. One of the challenges of using hypothermia was that previous experiments had shown a patient's body could only be maintained at a lower temperature for a limited amount of time before irreversible brain damage occurred due to a lack of oxygen reaching the brain. In the laboratory, Lewis had determined this time limit to be six minutes. This forced him to work extremely quickly and efficiently during his human open heart surgeries. Not surprisingly, heart transplantation could not be done within the rigid time constraints of hypothermia. An alternative way of allowing a cardiac surgeon to work on a heart was to stop the circulation of blood through the heart using a cardiopulmonary bypass machine. Also known as a heart-lung machine, the machine performs the functions of the heart and lungs by pumping oxygenated blood throughout the body to the vital organs and tissues. Dr. Clarence Dennis (1909-2005) was the first to attempt open heart surgery using this technique. As a child, he was very interested in building different machines; he built a radio, a record player, a lathe, and was fascinated by the Ford Model T automobile.

---

[24] Delbert G. Carlson and James M. Griffin, *Dog Owner's Home Veterinary Handbook* (New York: Howell, 1992), p. 407.

[25] Vincent L. Gott, "Lillehei, Lewis, and Wangensteen: "The Right Mix for Giant Achievements in Cardiac Surgery," *The Annals of Thoracic Surgery* 79 (2005), pp. S 2210-S 2213.

This interest continued well into his medical career. After observing the use of cellulose sausage casing in the first artificial kidney, invented by Dr. Willem J. Kolff (1911-2009), Dennis considered using the same material as a membrane to create a cardiopulmonary bypass machine to oxygenate blood. He travelled to Philadelphia to learn from Dr. John H. Gibbon, Jr. (1903-1973) who had been working on a heart-lung machine for more than 10 years. Using Gibbon's blueprints, Dennis returned to the University of Minneapolis where he began assembling a machine with the help of the university's machinists. Five years of research and experimentation with various prototypes resulted in a functional machine that allowed the circulation of blood to be maintained for over thirty minutes. The machine consisted of pumps, valves, switches, motors, a flow meter, a solenoid, a reservoir, and a series of slowly rotating stainless-steel disks.[26] Despite its complexity, the machine fit on a table and further testing convinced Dennis that his machine would be able to support a human patient's circulation while he repaired their heart.

Armed with his own cardiopulmonary bypass machine and four technicians present to run the machine during the surgery, Dennis operated on April 6, 1951, at the University Hospital in Minnesota on a six year old girl named Patricia Anderson (1945-1951). The operation went poorly after Dennis encountered a heart defect that was more severe than he had expected and the patient did not survive the operation. Anderson had been diagnosed with an atrial septal defect in June 1947 by a cardiologist at the University of Minnesota. However, accurate imaging techniques, such as computer tomography or magnetic resonance imaging, were not available at this time, and when her heart was exposed, Dennis discovered that her septum contained a number of holes as well as two malformed valves. Rather than a simple atrial septal defect, Anderson had a more complex defect in the atrioventricular canal which involved both of the heart's ventricles. Dennis sutured the largest hole closed, but the patient survived only for less than forty-five minutes after the cardiopulmonary machine was disconnected. Although the surgery was ultimately an unsuccessful disaster, Dennis believed that his machine had functioned properly and that the machine was not the cause of the patient's death.

Gibbon became the first to successfully use a cardiopulmonary bypass machine on May 6, 1953, in Philadelphia, Pennsylvania. He had worked for decades in the laboratory on his heart-lung machine and was rewarded for his efforts when he successfully repaired an atrial septal defect of an

---

[26] G. Wayne Miller, *King of Hearts* (New York: Random House Inc., 2000), p. 14.

eighteen-year old girl, Cecelia Bavolek, using the machine. He was able to maintain her circulation for twenty-six minutes while closing the hole in her heart wall. Fourteen years later, a cardiopulmonary bypass machine became also used during the first human heart transplantation. By 1960, hypothermia and cardiopulmonary bypass machines were used in combination by cardiac surgeons; and heparin was given to the patient before surgery to prevent blood clotting and the blood was cooled through the improved cardiopulmonary bypass machine to lower the body's basal metabolic rate, effectively decreasing the body's oxygen needs. Near the end of the surgery, the heat exchanger setting was changed to warm the blood and restore the patient's normal body temperature before the patient became disconnected from the cardiopulmonary bypass machine. Today, these fundamental techniques are still used to allow a bloodless and motionless field to be maintained, allowing a surgeon to work on a heart for upwards of six hours.

Maintaining Blood Oxygenation: The Use of Cross-Circulation

To repair atrial septal defects, Lewis used hypothermia in 1952 and Gibbon integrated the cardiopulmonary bypass machine in the operational setting in 1953. However, these were not the only two methods employed to maintain a patient's oxygenation during open heart surgery. For example, cross-circulation was developed as an alternate way of maintaining a patient's circulation during surgery. On March 26, 1954, Dr. Clarence Walton Lillehei (1918-1999) successfully repaired a more complex heart abnormality, a ventricular septal defect, using cross-circulation. Rather than using hypothermia, which was limited in its clinical uses, and unconvinced of the practicality of using a complicated cardiopulmonary bypass machine, Lillehei pioneered the technique of cross-circulation. An innovative surgeon and scientist, Lillehei significantly furthered the field of cardiac surgery and established many new techniques and procedures. His advances in cross-circulation created a safe and direct approach to repairing heart defects. For his accomplishments, Lillehei is commonly known as the "father of open heart surgery."[27]

Lillehei experimented with the use of cross-circulation in his laboratory using dogs before applying this technique to human patients. The primary objective of cross-circulation was to join the circulations of

[27] Denton A. Cooley, "C. Walton Lillehei, 'The Father of Open Heart Surgery," *Circulation* 100 (1999), pp. 1364-1365.

two dogs (and later two humans) through the use of pumps and tubes, allowing the donor animal to support the life of the patient animal. The theory behind this set-up was that it would enable the surgeon to work on the patient's heart to fix the heart's defects while adequately maintaining the patient's circulation. To maintain the patient's circulation, the donor's circulatory system played an essential role. By intimately joining the circulatory systems of the donor and the patient, the shared blood was oxygenated as it passed through the donor's lungs and was pumped through both circulations by the donor's heart, allowing the patient's organs and tissues to receive a constant supply of oxygenated blood. Lillehei and his research assistants were the first to demonstrate the use of cross circulation. Furthermore, they were able to create ventricular septal defects in dogs' hearts and then subsequently repair these defects using this technique. The dogs did very well after the surgeries, showing no signs of deterioration post-operatively. The dogs were euthanized after the experiments and on examination; their livers, kidneys, hearts, lungs, and brains were noted to be normal and healthy, proving that cross-circulation did not damage their organs and tissues. The results achieved in animal models were promising and Lillehei was optimistic that he could obtain similar results in human patients as well.

On March 26, 1954, Lillehei made the transition from the laboratory to the operating room when he first used cross-circulation in a human patient. His patient, thirteen-month-old Gregory Glidden (1953-1954), had a ventricular septal defect. Without repair, it was likely that the child's poorly functioning heart would fail and this would lead his death within the year. His father, Lyman Glidden, had consented to act as the donor patient once it had been confirmed that his blood was a match for his son. The Gliddens shared the O-positive blood group. During the surgery to fix his son's ventricular septal defect, Lyman's circulatory system would be connected to his son's to support his life. Despite the doubts of his colleagues, Lillehei believed this radical surgery would improve Gregory's prognosis. The hospital's Chief of Medicine, Dr. Cecil J. Watson (1901-1983) and Dr. Willis Potts (1895-1968), a well-recognized surgeon from the Children's Hospital in Chicago, did not approve of Lillehei's innovative surgery. In fact, Potts told Lillehei, "your name will go down in history as the first surgeon who has ever done an operation with 200 percent mortality."[28]

[28] Daniel A. Goor, *The Genius of C. Walton Lillehei and the True History of Open Heart Surgery*. 1st ed. (New York: Vantage Press, 2007), p. 4.

But Lillehei had the approval of Dr. Owen H. Wangensteen (1898-1981), the hospital's Chief of Surgery, and with this, he proceeded to perform the operation. To meet the oxygen demands of Gregory's body, his father's oxygenated blood was diverted through a tube from his femoral artery to his son's subclavian vein. Deoxygenated blood was collected from Gregory's body from his interior and superior vena cava and was shunted through a tube to his father's femoral vein, so that the blood bypassed Gregory's heart and lungs. From there, the blood travelled to Lyman's lungs for oxygenation, and was then subsequently diverted back to his son from a catheter in Lyman's femoral artery. The flow was regulated by a *Sigma Motor Pump*, keeping the volume of blood passing from father to son and from son to father equal. The Gliddens circulatory systems were intricately linked and were maintained carefully by four anaesthesiologists during the surgery. The father's circulation allowed oxygenated blood to reach Gregory's tissues and organs. The design of cross-circulation prevented blood from passing through Gregory's heart and lungs, allowing the surgeons to better visualize and work on his abnormal heart. A relatively bloodless operation field was successfully created and maintained throughout the surgery. Lillehei coined the term "controlled cross-circulation" for this technique.

On the day of the surgery, once Gregory's circulation was stabilized and completely came to depend on his father's heart function and circulation, Lillehei made a 2.5 cm incision in Gregory's right ventricle to gain access to the ventricular septal defect between the two ventricles that needed to be repaired to restore normal blood flow through Gregory's heart and body. Finding the hole, Lillehei stitched it closed, and then proceeded to close Gregory's chest. Next, the *Sigma Motor Pump* was turned off, the tubes connecting the Gliddens were removed, and their individual circulations were re-established. The cross circulation became effective, maintaining Gregory's circulation for nineteen minutes while he was connected to the pump. Gregory and Lyman Glidden did well after the surgery. However, a week after the surgery, Gregory developed pneumonia in his left lung. During the surgery, his left lung had been collapsed intentionally because the lung was not needed to oxygenate his blood since his father's lungs had taken over this function. By deflating his left lung, the surgeon could obtain superior access to his heart. The collapse of his lung was advantageous for the surgical repair of the heart, but at the same time the collapse may have increased Gregory's chances of acquiring pneumonia in the lung after the operation. Ten days after the surgery, at 9:15 am on April 6, 1954, Gregory died. On autopsy, it was revealed that his heart defect had completely healed and that the

pneumonia has been the cause of his death. This development paralleled Louis Washkansky's death later in 1967. In both cases, the heart surgeries were technically successful, but the pneumonias which emerged post-operatively led to the patients' deaths. While there had been great progress in the fight against organ rejection, further research and methods of detecting the early signs of rejection were clearly needed.

During the next four months, Lillehei performed similar surgeries on eight other children, repairing their ventricular septal defects using cross-circulation to maintain oxygenation of the blood during the operations. Six of the eight patients survived with good results and thirty-five years later, they are still alive and in good health. In total, Lillehei performed forty-five heart operations using cross-circulation. Despite Lillehei's success using cross circulation, however, other physicians continued to be sceptical of the technique. After Lillehei presented information about the recent surgeries he had performed using cross circulation at an international meeting in Montreal in May of 1954, Gibbon challenged Lillehei by claiming:

> We are still convinced that it is preferable to perform operations involving an open heart by procedures that do not involve another healthy person. There must be some risk to the donor in a cross circulation.[29]

And indeed this was the case. There had been donors who experienced cardiac arrests and other complications as a result of undergoing cross-circulation. Despite the criticism, Lillehei continued to perform ventricular septal repairs, and later began to repair the more complex tetralogy defects in paediatric patients – named after the French physician Étienne-Louis Arthur Fallot (1850-1911) – using cross-circulation. He also introduced the use of synthetic material, Ivalon or Teflon patches, to fill in the ventricular septal defects, rather than using primary closure where the two edges of the hole are brought together and sewn closed.[30]

The last surgery using cross-circulation was performed on July 19, 1955. The use of cross-circulation had led to many successful patient outcomes, but had also been constrained by the deaths of a number of patients and by adverse effects affecting donor patients. As Gibbon had predicted, involving two people in a single operation was not ideal and increased the chances of unfavourable outcomes and complications. In

---

[29] John H. Gibbon (1954), qtd. after: Daniel A. Goor, *The Genius of C. Walton Lillehei and the True History of Open Heart Surgery* (New York: Vantage Press, 2007), p. 11.

[30] Teflon is still used today to repair heart defects.

addition, cross circulation was not suitable for all patients because it placed an extra load on the donors' lungs and heart; and while this load could be managed to sustain the life of a child, it was less physiologically viable to maintain the larger demands of adult patients. Ultimately, the use of cross-circulation and hypothermia became less popular as the cardiopulmonary bypass machine emerged as the method of choice to maintain a patient's circulation while creating a bloodless and motionless surgical field. Nevertheless, cross-circulation and hypothermia allowed the realization of important surgical advancements and increased the understanding of human physiology. Valuable knowledge was acquired which helped the evolution towards the first human heart transplant.

As surgeons moved from treating simple pericardial effusions at the beginning of the nineteenth century to repairing complex congenital heart defects in the middle of the twentieth century, the potential for other therapeutic surgical interventions became more apparent. Different methods of maintaining blood oxygenation in patients were evaluated. Ultimately, the cardiopulmonary bypass machine proved to be a better option than the use of hypothermia or cross-circulation because it allowed greater control over oxygenation and its use was not limited by time and donor constraints. Advances in the field of cardiac surgery led to further innovations and the progression from open heart surgery to heart transplantation occurred over the span of fifteen years. Without the establishment of the surgical techniques to repair heart defects during the 1950s and early 1960s, it is unlikely that the first heart transplantation would have been possible in 1967.

The First Human Heart Transplantation: Culmination of Years of Experimentation and Development

The knowledge gained from a century of laboratory research, clinical experimentation, careful observation and trials of new therapies culminated in the achievement of the first human heart transplantation on December 3, 1967.[31] The technical surgical skills, which had been developed and refined over the years since the first heart surgery was performed in 1801, allowed heart transplantation to become technically successful. The development of open heart surgery and the extensive use of animal models importantly enabled surgeons' refinement of their techniques and preparation before attempting heart transplantation in human patients. Furthermore, the fact that surgeons were successful in

[31] Cf. Goor, *The Genius of C. Walton Lillehei*, p. 332.

transplanting other organs such as the kidney in 1954, made the prospect of heart transplantation more tangible and realistic. The success of kidney transplantation gave surgeons the boost in confidence that transplantation was indeed possible and that it was a valuable therapy option for patients with few other therapeutic options. The benefit that kidney transplant recipients had gained outweighed the harm of the operation and as a result; transplantation programs continued to grow and improve.

It is certainly that part of the successes of heart transplantation, which can be attributed to the pre-operative matching of the organ between the donor and the recipient. The ability to test and identify blood types and match organs between compatible donors and recipients dates back to Landsteiner's breakthrough discovery of blood types in 1901. Another important medical advancement that contributed to the successes of heart transplantation was the development of antibiotics and immunosuppressive medications used post-operatively to treat infections and prevent organ rejection. The major advancements that had been made in pharmaceutical therapies during the nineteenth century made these valuable medications available to Barnaard and other cardiac transplantation surgeons. The implementation of sterile procedures was another significant surgical innovation which played a role in the successful outcome of the world's first heart transplant recipient. The origins of aseptic techniques can be traced back to Lister in the 19th century, as was described above.

Heart transplantation would not have been possible if a bloodless and motionless operation field had not been attained to allow surgeons to work on patient's hearts effectively. The creation of the cardiopulmonary bypass machine was central in allowing a favourable surgical field to be created and heart transplantation would not have been possible in 1967 without this machine. Proper oxygenation is necessary to allow patients to undergo transplantation without sustaining irreversible brain damage. The accomplishment of hypothermia to help decreasing the oxygen demands of the brain led to the implementation of blood cooling through cardiopulmonary bypass machines. Although cross-circulation experienced some success in its clinical use, its surgical role continued to be limited because it necessitated putting a donor patient at risk in addition to the recipient patient. Alternative ways of oxygenating a patient's tissues and organs included the use a dog's lung, a self-lung, and an arterial reservoir, but these techniques all proved to be inferior to the oxygenation achieved using the more reliable and predictable cardiopulmonary bypass machines. Without the advancements in organ transplantations, surgical techniques, immunosuppressive medications, antibiotics and blood oxygenation over

the previous century, heart transplantation would not have been possible in 1967.

Heart Transplantation Research: Directions for the Future

Many developments have been made since Barnard delivered his talk entitled "Is Human Cardiac Transplantation Premature?" on March 2, 1968, at the annual meeting of the American College of Cardiology. He claimed that the medical demand for hearts would always outpace the supply of hearts available and indeed this has proven to be true. Barnard contended that the use of chimpanzee or gorilla hearts would provide an ideal way of ensuring a sufficient stock of donor hearts. While chimpanzees and humans share over 95 percent of the same chromosomes, we know today this type of transplantation is not a viable option. Dr. James Hardy (1918-2003) performed the first heart transplantation between a chimpanzee donor and a human recipient on January 23, 1964, at the University of Mississippi Medical Center. He had also been the first surgeon to perform a human lung transplant and was eager to become the first surgeon to perform a heart transplant in a human recipient. However, the chimpanzee's heart was too small to meet the demands of the recipient's body. The heart faltered within an hour of the transplantation. The medical community, the general public and many animal rights activists were very critical of Hardy's use of a chimpanzee due to the moral, ethical and health factors regarding the donor chimpanzee and human recipient. This virtually put an end to organ donations from animals.[32]

Today, over 40 years after Barnard performed the first human heart transplantation, scientists are considering the use of cell therapy to allow the re-growth and regeneration of failing hearts.[33] Organ rejection, the threat of infection, and the ability to replace a heart are no longer limitations to this life-saving technique. It is the lack of available organs that is the major constraint of heart transplantation. While 2,500 heart

---

[32] Gott, *The Right Mix for Giant Achievements in Cardiac Surgery*, pp. S 2210-S 2213.

[33] Paul W. M. Fedak, "Embryonic Stem Cells and Cardiac Regeneration," *Stem Cells and Development* 17 (2008), pp.1021-1022.

transplants are performed annually in the USA, there are 20,000 patients who could potentially benefit from the procedure.[34]

Cell therapy has shown human heart regeneration and functional enhancement in clinical trials using skeletal myoblasts and bone marrow-derived cells.[35] However, to date, no long-term benefits have been observed and any recognized benefits through the cell therapeutic approaches may be due to synergistic paracrine mechanisms rather than true cardiac regeneration. It has been observed, so far, that bone marrow cells do not differentiate into cardiac muscle or vasculature when injected directly into ischemic myocardium. Rather, they become mature hematopoietic cells and it is likely that these cells do not survive longer than a month after injection due to the short half-life of myeloid cells.[36]

Novel Cardiac Therapies: Past and Present

After Barnard successfully performed the world's first human heart transplantation, there was an enormous excitement internationally. The potential of this breakthrough therapy was perceived to be limitless and it was predicted that cardiac transplantation would save countless lives. Patients who had previously failed all available medical and surgical options suddenly developed newfound hope of survival. Surgeons around the world began performing heart transplantations. Astonishingly, following Barnard's landmark heart transplantation on December 3, 1967, 107 human heart transplants were performed by 64 surgical teams in 24 countries in 1968.[37] In the haste to save as many patients' lives as possible with this new effective technique, surgeons often neglected proper donor-recipient matching, anti-rejection therapy and follow-up care programs were frequently neglected, and proper surgical training was often inadequate prior to attempting these major operations.

---

[34] Leonard S. Lilly, ed., *Pathophysiology of Heart Disease*. 4th ed. USA (New York: Lippincott Williams and Wilkins, 2007), p. 258.

[35] Philippe Menasché, "Curent Status and Future Prospects for Cell Transplantation to Prevent Congestive Heart Failure," *Seminars in Thoracic and Cardiovascular Surgery* 20 (2008), pp. 131-137.

[36] Leora B. Balsam, Amy J. Wagers, Julie L. Christensen, Theo Kofidis, Irving L. Weissman, and Robert C. Robbins, "Haematopoietic Stem Cells Adopt Mature Haematopoietic Fates in Ischaemic Myocardium," *Nature* 428 (2004), pp. 668-673.

[37] Raymond Hofferberg, "Christiaan Barnard: His First Transplants and Their Impact on Concepts of Death," *British Medical Journal* 323 (2001), pp. 1478-1480.

The initial euphoria subsided as poor early results emerged. There was a great public outcry and widespread criticism, which put the future of heart transplantation into jeopardy. While the technical surgical skills existed to perform the procedures, the grafts were routinely being rejected. Many surgeons vowed to put an end to cardiac transplantation at their hospitals because at that time, the procedures nearly guaranteed the death of the transplant recipient. In fact, the cover of LIFE Magazine in 1971 highlighted "The Tragic Record of Heart Transplants" with pictures of the deceased recipients.[38] Rather than conceding defeat, Shumway went back to the laboratory and methodically began to develop protocols that allowed cardiac transplantation to become a validated, safe and useful procedure leading to successful patient outcomes. His work assured the future of heart transplantation as being a life-saving therapy and there is no doubt today that this therapy saves thousands of life every year. A similar phenomenon has been observed with the introduction of cell therapy. Initially, there was great enthusiasm and anticipation about this novel method of regenerating failing hearts. However, this may have been premature as there has been little benefit to patients to date from the use of cell therapy. But following Shumway's example, researchers and clinicians have returned to the laboratory to learn more about cell regeneration and to refine its therapeutic uses. Cell transplantation holds enormous potential, yet as the problematic history of heart transplantation has proven, years of dedicated research and experimentation are necessary before new therapies can be validated and before they become valuable and effective options for patients. The initial excitement surrounding heart transplantation was followed by the great outcry against it; and finally the eventual success of the treatment did prove the importance of thorough research and development before leaping into the implementation of widespread novel therapies in clinical practice.

Conclusions

The road to the first human heart transplant was long and convoluted, with surgeons from the United States of America, Europe, Russia, and South Africa all striving to be the first to perform a successful surgery and achieve "medical immortality". From Shumway and Lower to Gibbon and Dennis to Lillehei and Barnard, there were many important cardiac surgeons who helped pave the way to the first human heart transplantation.

---

[38] "The Tragic Record of Heart Transplants," *LIFE Magazine* (Sept. 17, 1971), pp. 1-29.

The cardiac surgeons involved in heart transplants were critical in developing the surgical technique, yet equally important were the researchers and physicians who achieved the major medical milestones that allowed heart transplantation to be successful and therefore beneficial to the general public.

Kidney transplantation experiences confirmed that solid organ transplantations were both viable and valuable therapeutic techniques. The successes of kidney transplantations encouraged the development of cardiac transplantation programs in numerous hospitals. ABO blood type matching, the discovery of immunosuppressive and antibiotic medications, and the development of the cardiopulmonary machine were significant discoveries that contributed to the field of cardiac surgery and to medicine in general. Laboratory experimentation and clinical trials with hypothermia and cross circulation helped to expand knowledge of physiologic regulation and to emphasize the importance of blood oxygenation. Animal models were invaluable to the progress of heart surgery and cardiac transplantation. Decades of dedicated research and committed laboratory work culminated in the first human heart transplantation on December 3, 1967; by 1997, more than 40,000 heart transplants had been performed across the globe.[39] Advances in surgical technique, patient care, and pharmacology have increased survival odds. According to the American Heart Association (AHA), as of June 15, 2007, the one-year survival rate was 87.4 percent for males and 85.5 percent for females, while the five-year survival rate was 72.3 percent for males and 67.6 percent for females following heart transplantation.[40]

Today, 4,000 transplants are performed annually around the world and virtually any sized heart can be transplanted. Dylan Stork (b. 2000), a seven-week old boy weighting 2.5 kilograms, became the world's smallest heart transplant recipient when he received a new heart at Loma Linda University Medical Center in Loma Linda, California in 2000. At the University of Alberta Hospital in Edmonton, also the Canadian province of Alberta made history – in 1999 – when a heart transplant was performed in a 79 year old recipient, making him the oldest heart transplant recipient in history. According to the 2001 "Canadian Cardiovascular Society Consensus Guideline Update for the Management and Prevention of Congestive Heart Failure", over 350,000 Canadians are living with congestive heart failure and up to 25 percent to 40 percent of

---

[39] BBC News, *Thirtieth Anniversary of Heart Transplants. 1997*; retrieved 22 October 2008 (news.bbc.co.uk/1/hi/sci/tech/36604.stm).

[40] American Heart Organization, *Heart Transplants: Statistics. 2007*; retrieved 1 January 2009 (http://www.americanheart.org/presenter.jhtml?identifier=4588).

people die within one year of diagnosis.[41] Cardiac transplantation is the only option for those who have failed medical therapy and exhausted other surgical options. Even though cardiac transplantation is proven possible and effective in treating congestive heart failure, it still poses more problems for surgeons and patients alike. In order for cardiac transplantation to be truly effective, surgeons, physicians and researchers must solve the problem of ensuring that there are enough donor hearts to go around for those who desperately need them so that they do not die before they are matched to a suitable donor heart.

[41] Peter Liu, "Canadian Cardiovascular Society Consensus Guideline Update for the Management and Prevention of Congestive Heart Failure," *The Canadian Journal of Cardiology* 17 (2001), pp. E5-E48.