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Abstract

The University of Minnesota has a unique history relative to advances in cardiovascular research, surgery, and the development of medical devices. Interestingly, the writing of this textbook coincides with two important anniversaries in cardiovascular medicine at the University. Sixty years ago, in 1954, cross-circulation for intracardiac operations was first introduced, sparking a number of innovations in the area of open-heart surgery. Additionally, in 2014, the University of Minnesota celebrated the 800th heart transplant performed since 1978 and sustains one of the longest-running heart transplant centers in the world. In this chapter, we will review some of this history and how it has led to the creation of a dynamic medical device industry in the state of Minnesota and surrounding regions.

Keywords

Medical device development • Cross-circulation • Bubble oxygenator • Pacemaker • Heart valves

25.1 Introduction

The era from 1950 to 1967 was an incredible time of innovation at the University of Minnesota's Department of Surgery in the newly emerging fields of open-heart surgery and medical devices. There were many reasons for this, but most importantly (1) the university had excellent facilities, including a unique privately funded 80-bed heart hospital for pediatric and adult patients (this Variety Club Heart Hospital was the first dedicated heart hospital in the USA) (Fig. 25.1) and (2) the Department of Surgery was chaired by Owen H. Wangensteen, M.D., a leader who "created the milieu and the opportunities for great achievements by many of his pupils" and was considered the "mentor of a thousand surgeons" (Fig. 25.2 and Table 25.1) [1]. More specifically,

Dr. Wangensteen encouraged his medical students, residents, and junior faculty to "step out of the box," innovate, and solve problems in different ways. In other words, take action and not assume that those who went before them had all the answers. He also believed strongly in collaborations with the basic science departments, specifically the Department of Physiology whose department head, Maurice Visscher, played an integral role in supporting both research and the clinical training of surgical residents. To that end, Wangensteen instituted a 2-year research program for all residents; this surgical Ph.D. program was the only one in the country at its inception, and students were required to take various advanced physiology courses offered through the Department of Physiology.

In the early 1950s, the innovative surge was credited to the fact that many surgical residents were returning from World War II, where they had experienced life and death situations when managing surgical field units. They had little or no fear of death and their generation was not afraid to "push the envelope" to help patients. By today's standards, these residents would be viewed as mavericks but, in fact, they had little to lose, not unlike situations they faced on the

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Fig. 25.1 John Dilorio (Dr. Iaizzo's cousin) was a young cardiac patient of Dr. Lillehei and his team, shown here in 1958 (a) in his hospital bed at the University Variety Club Hospital and then (b) leaving the hospital with his father

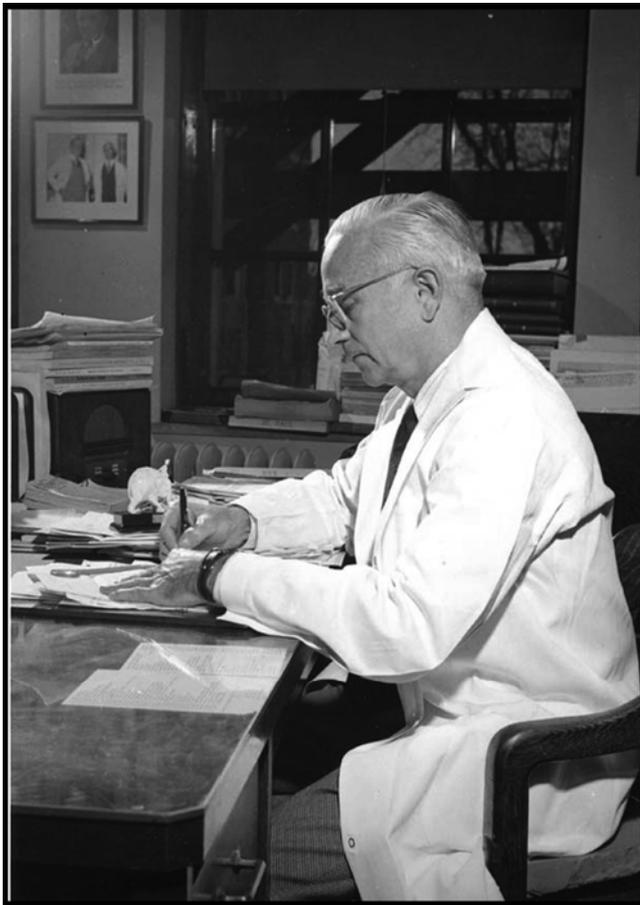
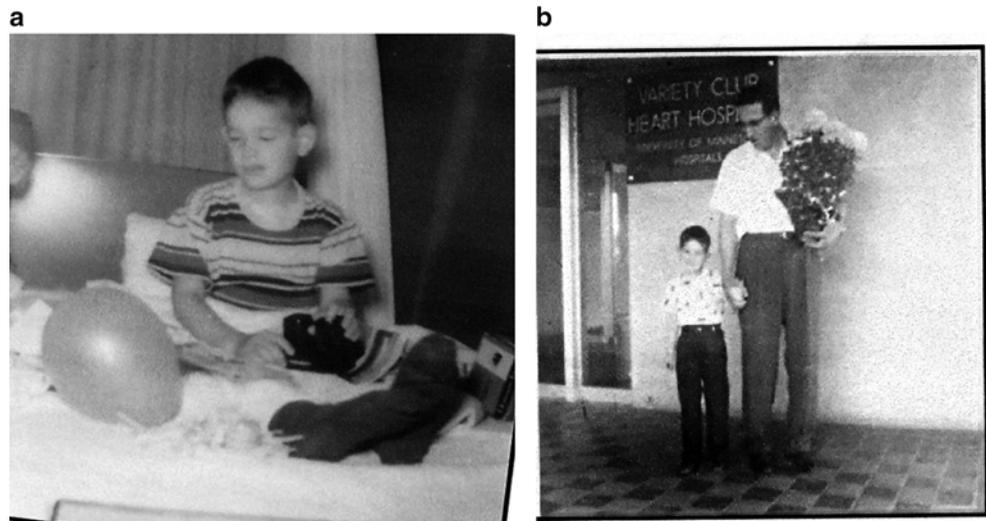


Fig. 25.2 “The Chief” Owen H. Wangensteen, the youngest Surgery Department Chairman at age 31, served as chairman of the department from 1930 to 1967

battlefield. Their heart patients were dying and/or had little chance of survival without the novel techniques that were successfully implemented in Minnesota.

One of these young war-experienced surgeons was C. Walton Lillehei, who returned to the University of Minnesota in 1950 to complete his surgical residency after leading an army surgical field unit in both North Africa and Italy (Fig. 25.3). Lillehei was very bright (he also completed M.S. and Ph.D. degrees during this time) and was known as an impulsive maverick, always pushing to the next level of care for his clinical patients for whom he had great empathy. Lillehei and his team launched many surgical innovations during this period, primarily due to their hands-on research experience in the experimental dog laboratories; one site for this research was located in the basement of the Mayo Hospital building, just three floors below the main operating rooms. Today, this lab space houses the Visible Heart® Laboratory under the direction of Dr. Paul Iaizzo (Figs. 25.4 and 25.5) [2].

Interestingly, prior to 1950, the heart was considered to be the core of human emotion, even the soul itself. For perspective, Table 25.2 depicts some highlights of a typical operating room in the 1950s. Relative to open-heart surgery in 1951, congenital heart defects were responsible for 1 % of all deaths in this age group; thus the prognosis was poor for a child with such a defect. There were no methods for conducting external heart surgery and no way to oxygenate the brain during surgery. In other words, attempts were made to repair a patient's heart while it remained beating, obscuring the view with blood; any stoppage of blood flow would result in damage of the brain. Therefore, only the simplest surgeries could be performed on the beating heart.

When the medical profession eventually began to view the heart more physiologically, as a pump or machine within the body, researchers and clinicians began to develop new ways to repair and replace worn-out parts of the heart. Innovations in the field of cardiac surgery then flourished (Table 25.3). Such innovation became prominent at the University of

Table 25.1 Department of Surgery at the University of Minnesota: chairs/interim heads

Surgery Department chair/interim head	Position	Years served
Arthur C. Strachauer	Department Chair	-1925, 1927–1929
Owen H. Wangenstein	Department Chair	1930–1967
John S. Najarian	Department Chair	1967–1993
Edward W. Humphrey	Interim Chair	1993–1994
Frank B. Cerra	Interim Chair	1994–1995
David L. Dunn	Department Chair	1995–2005
David A. Rothenberger	Interim Chair	2005–2006
Selwyn M. Vickers	Department Chair	2006–2013
David A. Rothenberger	Department Chair	2013–present

**Fig. 25.3** Walt Lillehei in his army uniform

Minnesota. For example, Dr. Clarence Dennis designed one of the first heart–lung machines for total cardiopulmonary bypass, which was subsequently tested successfully on dogs (Figs. 25.4 and 25.6). However, when Dennis and his team used the heart–lung machine in the clinical area for the first time on April 5, 1951, the patient died due to complications; a second patient also died during surgery from a massive air

embolism. Not long after, Dr. Dennis moved his machine and most of his team to New York City [1].

Worldwide, one of the next major milestones in cardiac surgery was the first open-heart surgery performed using hypothermia, a procedure first attempted on September 2, 1952, by Drs. F. John Lewis and Richard Varco and colleagues at the University of Minnesota (Figs. 25.4 and 25.7). This procedure, proposed by Dr. W.G. Bigelow of Toronto, lowered the body temperature of patients 12–15 °F to reduce their blood flow, thereby reducing the body’s need for oxygen. Brain cells would die after 3–4 min at normal temperature without oxygen, but hypothermia allowed the University of Minnesota team (Drs. F. John Lewis, C. Walton Lillehei, Mansur Taufic, and Richard Varco) to successfully complete a 5½-min repair of the atrial septum of a 5-year-old patient. This was recognized as a significant landmark in the history of cardiac surgery; until this time, no surgeon had succeeded in opening the heart to perform intracardiac repair under direct vision. Hypothermia with inflow stasis proved to be excellent for some of the less complicated surgical repairs, but it was not a viable option for more extensive cardiac procedures. Major drawbacks of this approach at that time were the inability to rewarm a cold, nonbeating heart and the lack of clinical defibrillators [3].

From a historic perspective, another key milestone in cardiac surgery, though not accomplished at the University of Minnesota, occurred on May 6, 1953 when Dr. J. Gibbon closed an atrial septal defect using a pump oxygenator for an intracardiac operation. Although this first success with the pump oxygenator was well received, it aroused surprisingly little excitement or enthusiasm among cardiologists and cardiac surgeons at that time, likely because other centers had launched their own experiments with bubble oxygenators. Interestingly, Gibbon was never able to repeat his one clinical success; he ultimately became discouraged and did not use the pump oxygenator again.

During this era, “there was a common scenario, namely, good results with acceptable survival in the experimental animals but nearly universal failure when the same apparatus and techniques were applied to human beings [3].” Furthermore, it was written that “many of the most experienced investigators concluded with seemingly impeccable logic that the problems were not with the perfusion techniques or the heart lung machines [3]. Rather, they came to believe that the ‘sick human heart’ ravaged by failure, could not possibly be expected to tolerate the magnitude of the operation required and then recover with good output, as occurred when the same machines and techniques were applied to healthy dogs [3].” It is important to consider that these experimental animals were typically healthy dogs and that anatomical differences between canine and human hearts may have been a significant distinguishing factor (see Chap. 6).

Fig. 25.4 Schematic of “cardiovascular firsts” at the University of Minnesota

CARDIOVASCULAR FIRSTS

1951 World's first open-heart surgery using a heart/lung machine (Dennis)

1952 World's first atrial-septal defect closure using deep hypothermia (Lewis & Varco)

1954 World's first procedures using cross-circulation:
 • Ventricular-septal defect closure (Lillehei, Cohen & Warden)
 • Atrio-ventricular canal correction
 • Tetralogy of Fallot correction (Lillehei)

1955 First disposable bubble oxygenator (DeWall)

1955 First use of direct ventricular pacing (Gott & Lillehei)

1958 First battery-operated wearable pacemaker (Bakken & Lillehei)

1968 First mechanical heart valves developed (Lillehei-Kalke)

1970 First implant of St. Jude bi-leaflet valve

1997 Start of the Visible Heart® Laboratory

1997 First annual "Bakken Surgical Device Symposium"

2000 Atlas of Human Cardiac Anatomy launched online

2007 Medical Devices Center opens



Fig. 25.5 Photo of Dr. Paul Iaizzo in the Visible Heart® Laboratory at the University of Minnesota

Table 25.2 1950s operating room environment

- No computers or digital equipment existed
- Glass thermometers, blood pressure cuffs, and a finger pressed against the wrist were used to obtain vital signs
- Anesthesia was supplied on a soaked rag and delivered by squeezing the black bag
- (Nonoperating room) X-rays were the only imaging equipment available
- Flammable gases could cause explosions in the operating room
- Head lamps lit the operative field
- The second hand on a wall clock was one of the most useful instruments to a surgeon
- No pulse oximeters, pacemakers, blood-gas analyzers, or specialized imaging existed

25.2 Cross-Circulation

Extracorporeal circulation by controlled cross-circulation was introduced clinically on March 26, 1954, after much animal experimentation (Figs. 25.4 and 25.8). The use of cross-circulation for intracardiac operations was an immense departure from established surgical practice at the time and was considered as a major breakthrough that motivated numerous innovations in the area of open-heart surgery [4].

The thought of taking a normal healthy human being into the operating room to provide donor circulation was considered “unacceptable and even immoral” by some critics. The risks to the donors included blood incompatibility, infection, air embolism (stroke), and/or blood volume imbalances.

From March 1955 onward, three additional bypass methods were introduced and successfully used, including (1) perfusion from a reservoir of arterialized blood, (2) heterologous (dog) lungs as an oxygenator, and (3) the Lillehei–DeWalt disposable bubble oxygenator [3]. Yet, many believe that the single most important discovery that contributed to the success of clinical open-heart operations was the realization of the vast discrepancy between the total body flow rate *thought* necessary and what was *actually* necessary to maintain cerebral viability. Lillehei and his team are credited with applying the findings of two British surgeons (Andreasen and Watson) who identified the *azygos factor*—the ability of dogs to survive up to 40 min without brain damage when all blood flow was stopped except through the azygos vein. Specifically, Morley Cohen and Lillehei hypothesized that when blood flow was low, the blood vessels dilated to receive a larger share of the blood, while the tissues absorbed a much higher proportion of the oxygen as compared to normal circulation [3]. Previously, it was thought that basal or resting cardiac output at 100–160 ml/kg/min was safe maintenance during cardiopulmonary bypass. The azygos flow studies showed that 8–14 ml/kg/min maintained the physiological integrity of the vital centers, but Lillehei added a margin of safety and set his basic perfusion rate at 25–30 ml/kg/min. This approach reduced excessive complications of blood loss, excessive hemolysis, abnormal bleeding, and/or renal shutdown [3].

Altogether, 45 patients (aged 5 months to 10 years) underwent open-heart surgery with the cross-circulation approach at the University in 1954–1955; prior to these pioneering surgeries, such patients were considered to have lesions that were hopelessly unrepairable. Of this group, 22 (49 %) of the patients lived to be long-term survivors (greater than 30 years) and lead normal productive lives; 11 of the female long-term survivors subsequently gave birth to a total of 25 children who were free from any congenital heart defects. In addition, all 45 donors survived, with only one donor experiencing a major complication. At a more recent 53-year follow-up, 20 (44 %) of the original cross-circulation patients were living with no problems or significant limitations related to their original surgeries [5].

During this period of time, an intense competitive/collaborative relationship existed between the University of Minnesota and the Mayo Clinic (Rochester, MN, USA), the only other primary site where open-heart surgery was being performed. Lillehei recalled in his interview with G. Wayne Miller (author of *King of Hearts*) that the Mayo Clinic operated 7 days a week, so on Saturdays when Lillehei’s team

Table 25.3 University of Minnesota milestones

1887	New standards requiring medical students to pass exams and gain medical examining board approval (led by Medical School Dean, Perry Millard)
1911	Minnesota became the first state to mandate hospital internships for medical students
1930s	Discovery of the link between cholesterol and heart disease (Ancel Keys)
1950	First adaptation of the mass spectrograph (Alfred Nier)
1951	First attempt to use a heart–lung machine (Clarence Dennis)
1952	First successful open-heart surgery using hypothermia (F. John Lewis)
1953	First jejunoileal bypass (Richard L. Varco)
1954	First open-heart procedure using cross-circulation (C. Walton Lillehei)
1954	First surgical correction of tetralogy of Fallot (C. Walton Lillehei)
1955	First successful use of the bubble oxygenator (Richard DeWall)
1958	First use of a small, portable battery-powered pacemaker (Earl Bakken)
1963	First human partial ileal bypass (Henry Buchwald)
1966	First clinical pancreas transplant (William D. Kelly and Richard C. Lillehei)
1966–1968	First prosthetic heart valves (Lillehei–Nakib toroidal disk in 1966, Lillehei–Kaster pivoting disk in 1967, Kalke–Lillehei rigid bileaflet prosthesis in 1968)
1967	Bretylum, a drug developed by Marvin Bacaner, saved the life of Dwight Eisenhower
1967	World’s first heart transplant (Dr. Christiaan Barnard, trained by C. Walton Lillehei)
1968	First successful bone marrow transplant (Robert A. Good)
1969	Invention of implantable drug pump (Henry Buchwald, Richard Varco, Frank Dorman, Perry L. Blackshear, Perry J. Blackshear)
1976	Medical Device Amendment to FDA Cosmetic Act
1977	First implant of St. Jude mechanical heart valve at University Hospital
1978	Human heart transplantation was performed at University
1978	Pediatric human heart transplantation was performed at University Hospital (Ernesto Molina)
1988	HDI/Pulse Wave® profiler founded (Hypertension Diagnostics, Inc., Jay Cohn, Stanley Finkelstein)
1993	Angel Wings® transcatheter closure device invented (Gladwin Das)
1994	First successful simultaneous pancreas–kidney transplant using a living donor (David Sutherland)
1995	Amplatzer® Occlusion Devices founded (AGA Medical Corp., Kurt Amplatz)
1997	First kidney–bowel transplantation (Rainer Gruessner)
1999	CardioPump Device evaluated (Keith Lurie, et al.)
2000	University’s Medical School has produced more family doctors than any other institution in the USA
2003	Robotic cardiac surgery performed at the University of Minnesota (Kenneth Liao)
2005	Launch of free-access website “Atlas of Human Cardiac Anatomy” (Visible Heart Laboratory; www.vhlab.umn.edu/atlas)
2006	Implant of left ventricular assist device using minimally invasive approach (Kenneth Liao)

was not scheduled for surgery, they would travel to the Mayo Clinic and watch Dr. John Kirklin and his colleagues (Miller, G.W., Transcriptions of audio tapes for *King of Hearts*, University of Minnesota Archives) [6]. Dr. Kirklin was successfully using a modification of the Gibbon heart–lung machine, and after observing his achievements, Lillehei began a slow transition away from cross-circulation and toward using a heart–lung machine of his own design (Figs. 25.4 and 25.9). In the beginning, Lillehei used the heart–lung machine for simpler, more straightforward cases and continued using cross-circulation for more complicated surgeries. Although its clinical use was short lived, cross-circulation is still considered today as one of the most important stepping stones in the development of the discipline of cardiac surgery.

25.3 Lillehei–DeWall Bubble Oxygenator

Importantly, John Gibbon, M.D., from Boston, invented the cardiopulmonary bypass procedure and performed the first intracardiac repair using extracorporeal perfusion in 1953. His bubble oxygenator, which looked surprisingly like a computer, was manufactured and financed by IBM. His reported achievements stimulated rapid development of the knowledge base and equipment necessary for both accurate diagnoses of cardiac disease and successful intracardiac operations. Yet at that time, it was recognized that the main problems with film oxygenators were (1) poor efficiency, (2) excessive hemolysis, (3) large priming volumes, and (4) development of bubbles and foam in the

Fig. 25.6 Clarence Dennis with the first heart–lung machine at the University of Minnesota

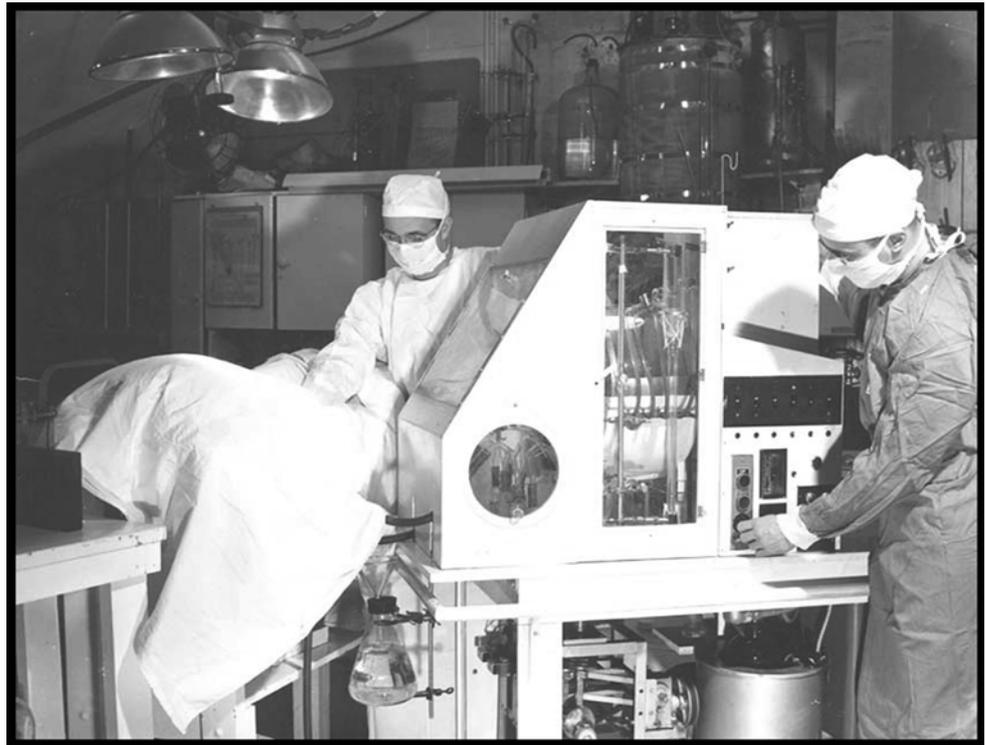


Fig. 25.7 In this 1952 photo, Richard L. Varco (left) and F. John Lewis stand behind the hypothermia machine that they used during the world's first successful open-heart surgery



blood. All designs required blood flows of $2.2 \text{ l/m}^2/\text{min}$, usually three to four units of blood for priming and another two units for the remainder of the circuit. Furthermore, after each use, the machine needed to be broken down,

washed, rinsed in hemolytic solution, reassembled, resterilized, and reconfigured.

During this era, Richard DeWall came to work at the University of Minnesota as an animal attendant in Lillehei's

Fig. 25.8 Diagram of cross-circulation

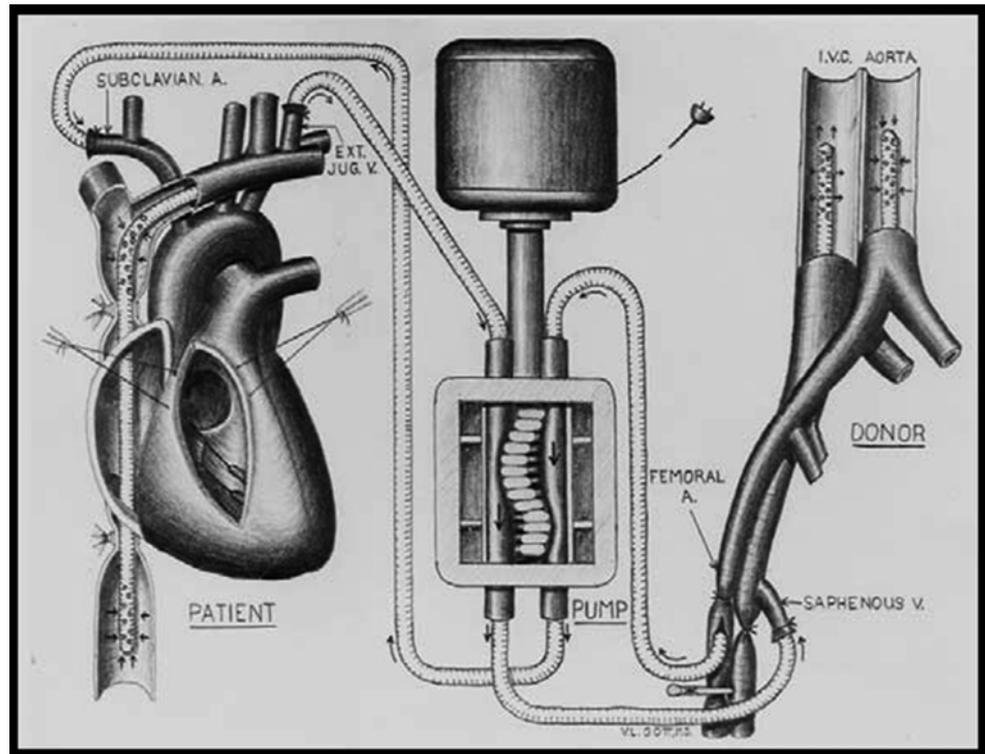
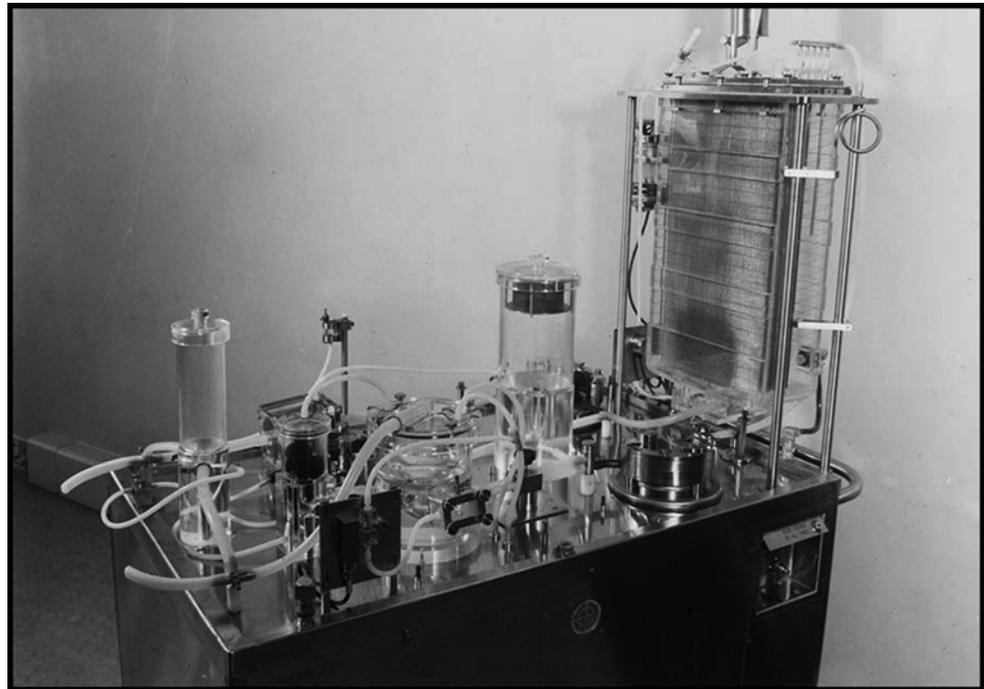


Fig. 25.9 Mayo Clinic's heart-lung machine was as big as a Wurlitzer organ; it cost thousands of dollars and required great skill to operate



research laboratory. It was noted that DeWall would manage the pump while the anesthesiologists would take breaks, and soon he began to take an interest in the problems associated with oxygenating blood. Eventually, Lillehei challenged DeWall to find a way to eliminate bubbles in the oxygenator procedure. Importantly, DeWall brought to fruition a dramatic

technological breakthrough in 1955 by developing the first bubble oxygenator with a unique method for removing bubbles from the freshly oxygenated blood (Figs. 25.4 and 25.10). In DeWall's design, blood entered the bottom of a tall cylinder along with oxygen passed through sintered glass to create bubbles. As the bubbles and blood rose, gas exchange

Fig. 25.10 University of Minnesota's bubble oxygenator cost \$15 and was easy to use. Richard DeWall is shown here with his model in 1955



occurred at the surface of each bubble. At the top of the cylinder, arterialized bubble-rich blood passed over stainless steel wool coated with silicone antifoam; it then traveled through a long helical settling coil to allow bubbles to slowly rise and exit the blood.

Two important components in the Lillehei–DeWall bubble oxygenator were the tubing and the silicon antifoam solution. The tubing was Mayon polyethylene tubing (typically used in the dairy and beer industries and specifically in the production of mayonnaise) available from Mayon Plastics, a company whose CEO was a classmate of Lillehei's and a graduate of the University's chemical engineering program. The silicone antifoam solution, Antifoam A, was used to coat the tubing to prevent foaming of the liquids being transported.

The oxygenator was wonderfully efficient; experimental animals (and later patients) did not show detectable effects of residual gas emboli. More importantly, this design eventually led to the development of a plastic, prepackaged, disposable, sterile oxygenator that replaced the expensive stainless steel, labor-intensive screen, and film devices. An economic and reliable oxygenator had arrived and the medical industry began to consider using disposable components for the heart–lung machine.

Two years after its introduction, the Lillehei–DeWall bubble oxygenator had been used in 350 open-heart operations at the University of Minnesota. DeWall steadily improved the device through three models, but it remained a very simple, disposable, heat-sterilizable device that could be built to accommodate only the amount of blood required for each patient and then discarded.

In 1956, another one of Lillehei's residents, Vincent Gott, invented a bubble oxygenator in which DeWall's helix design was flattened and enclosed between two heat-sealed plastic sheets (Fig. 25.11). This sheet bubble oxygenator proved to be the key to widespread acceptance of the device in open-heart surgery, because it could be easily manufactured and distributed in a sterile package and it was inexpensive enough to be disposable. The University of Minnesota eventually licensed the rights to manufacture and sell the device to Travenol, Inc. With the bubble oxygenator and techniques developed by Lillehei and his colleagues, the University of Minnesota had become even more prominent for making open-heart surgery possible and relatively safe [7].

By coincidence, Dr. Paul Iaizzo has a cousin, John Dilorio, who had a ventricular septal defect repaired by Dr. Lillehei in 1958, and a bubble oxygenation system was utilized during his surgery (Fig. 25.1). Interestingly, John's family journaled

Fig. 25.11 Richard DeWall and Vincent Gott look at the first commercially manufactured sterile bubble oxygenator in 1956



during his stay at the university's Variety Club Heart Hospital and noted the following events: (1) admitted to Variety Club Hospital on May 26, 1958; (2) surgery date of June 11, 1958, with a 6:45 start; (3) brought patient to the recovery room at 14:00; (4) treated postsurgically within an oxygen tent for 24 h and a cold room for 5 days; and (5) discharged on July 2, 1958. John is still alive today living in Texas, another testimony to the legacy of Dr. Lillehei.

25.4 Heart Block and the Development of the Pacemaker

An unexpected clinical consequence of the development of open-heart surgery was the discovery of a revolutionary new concept for treatment of complete heart block. Heart block is typically defined as the inability of electrical impulses that begin high in the right atrium to reach the ventricles. Deprived of their normal signal, the ventricles may beat slowly on their own (escape rhythm) or not at all; any prolonged decrease in heart rate that limits a patient's normal activity will typically result in heart failure. At that time, with the only existing treatment for complete block being positive chronotropic drugs or electrodes applied to the surface of the chest, there were no 30-day survivors.

Fortunately, in 1952, Paul Zoll, a cardiologist in Boston, invented the first pacemaker unit, which was a large tabletop external unit with a chest electrode. It was successfully used to resuscitate patients in the hospital, but required the transcutaneous delivery of 50–150 V, which was incredibly painful for children and typically left scarring blisters.

Complete heart block developed in 10–20 % of Dr. Lillehei's early patients undergoing closure of ventricular septal defects (e.g., due to induced injury of the heart's conduction system by stitches) and, unfortunately, hospital mortality was 100 % in this group of patients. Importantly, early fatality from heart block was completely eliminated with the use of a myocardially placed electrode in combination with an external plug-in electric stimulator [8]. This method of treatment, suggested by Dr. John A. Johnson, a professor of physiology at the University of Minnesota, required electrical stimuli of small magnitude (5–10 milliamps and 1–2 V) and provided very effective control of the heart rate. Such an approach was almost painless but, at that time, it required an AC electrical source, thus limiting the mobility of the patient to the length of the extension cord. It was first used by Dr. Lillehei on a patient on January 30, 1957; subsequently an 89 % survival rate for patients with prior heart block was reported (Fig. 25.4). More specifically, the pacemaker approach employed a multistrand, braided stainless steel wire in a Teflon sleeve that was directly implanted into the ventricular myocardium, with the other end brought through the surgical wound and attached to external stimulation. The first pacemaker (pulse generator) was a Grass physiological stimulator borrowed from the university's Physiology Department. This procedure was designed for short-term pacing, with removal of the wires 1–2 weeks after the heart regained a consistent rhythm.

The surgical operating rooms in the 1950s were equipped with EKG and pressure-monitoring devices, and the vacuum tubes required frequent monitoring and maintenance to keep them running and calibrated. Hence, the University Hospital

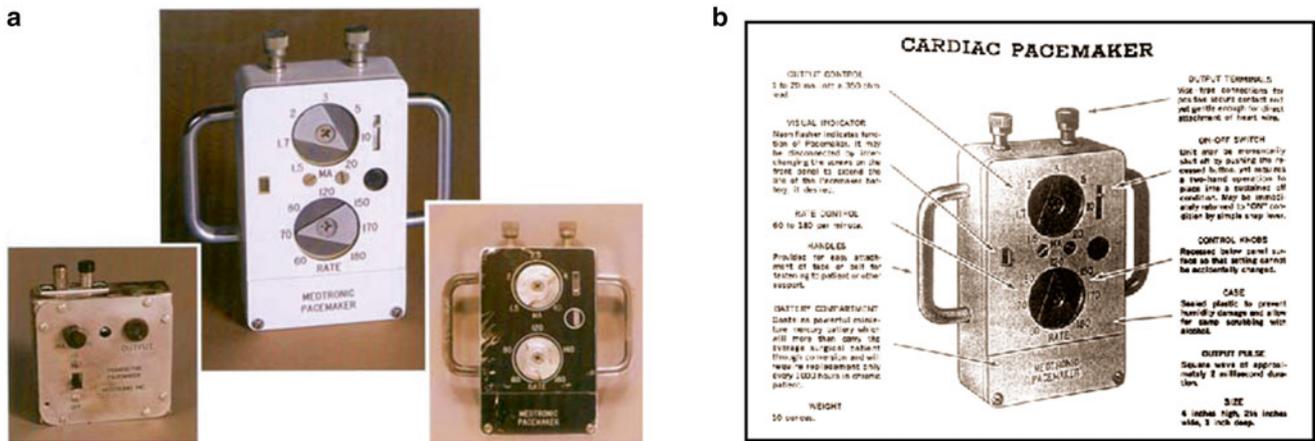


Fig. 25.13 (a) The first pacemaker prototype (left), the “black box” 5800 external pacemaker (the preliminary test model, right) and the “white box” 5800 production model (center). (b) A page from the Medtronic catalog advertising the 5800 pacemaker

pacemaker became implantable and redefined for long-term pacing use (Fig. 25.14). Nevertheless, the 5800 pacemaker became the symbol for Medtronic’s shared belief in medical progress through technology; this was celebrated during an unveiling of a bronze statue of Earl Bakken holding the 5800 pacemaker at his retirement celebration in 1994. Years later, the 5800 was viewed by Lillehei as a technological watershed—it fostered interdisciplinary collaboration and exemplified the productive and successful marriage of medicine and technology.

Both Lillehei and Bakken have named professorships at the University of Minnesota. In addition, the Lillehei Heart Institute (LHI) was created in 2002 to honor the past with the C. Walton Lillehei Museum, while supporting the future through its unique research and educational programs. LHI is an interdisciplinary institute within the Academic Health Center and Medical School at the University of Minnesota, made possible by a generous gift from Kaye Lillehei, wife of C. Walton Lillehei. Dr. Daniel Garry, Chief of the Cardiovascular Division of Medicine, was named Director of the LHI in 2007. The LHI has flourished since its inception, and a new cardiovascular research building/facility opened in the University’s Bioscience District in 2013; this facility is the home of numerous dedicated basic and applied scientists working on the next innovative breakthroughs in cardiovascular medicine.

More specifically, guided by a vision to sustain and enhance world leadership in the prevention, detection, and treatment of heart and vascular diseases, LHI supports these important efforts [10]:

1. Clinical and basic science research focused on cardiovascular genomics, heart development, heart regeneration, stem cell therapies, personalized medicine, heart failure, vascular biology, and device design to treat cardiovascular diseases. In recent years, LHI has established and

recruited new research teams that work in their new state-of-the-art research facilities.

2. Participation as the Midwestern hub of the National Heart, Lung, and Blood Institute’s (NHLBI) Progenitor Cell Biology Consortium, commissioned to lead new cardiovascular therapies.
3. LHI Lecture Series (established in 2003). In addition to showcasing leading edge research taking place at the University of Minnesota, the weekly lecture series invites scientists from institutions across the USA and abroad to share their research.
4. Summer Research Scholars Program. Annual summer research scholarships in basic science related to cardiovascular disease are awarded to highly qualified high school and undergraduate students. These highly competitive, prestigious scholarships are designed to expose students to several disciplines within cardiovascular disease research and its clinical applications.
5. Lillehei Endowed Scholars Program. This program provides cardiovascular and respiratory research fellowships and grants to University of Minnesota faculty and students, including undergraduates, medical students, and predoctoral and postdoctoral fellowships.
6. “A Heart to Learn” Youth Educational Program. Hosted by faculty, staff, and graduate/medical students from the Visible Heart Laboratory [2], this community outreach program is designed to teach concepts of cardiac anatomy, physiology, medical devices, and heart health to students in elementary, middle, and high schools.

In December 2007, at a celebration of the 50th anniversary of the wearable, battery-powered pacemaker, the University of Minnesota awarded Earl Bakken with an honorary M.D. degree (Fig. 25.15). In the same month, the University’s Department of Surgery hosted the first annual Bakken Surgical Device Symposium to celebrate this legacy.

Fig. 25.14 Dr. Samuel Hunter (*inset*) and adult pacing patient Warren Mauston. Dr. Hunter and Medtronic engineer Norman Roth developed a bipolar electrode that represented a major advance in pacing technology. First implanted in 1959, the Hunter–Roth lead helped contribute 7 years of life to a Stokes–Adams disease patient, Warren Mauston in 1960



Fig. 25.15 Earl Bakken, the founder of Medtronic Inc., received an honorary M.D. degree from the University of Minnesota in 2007. He is shown here with his M.D. white coat and medical bag, presenting his historic prospective lecture at the first Bakken Surgical Device Symposium, hosted by the Department of Surgery at the University of Minnesota on December 13, 2007

Since its inception, this symposium has focused on various topics related to cutting-edge medical devices including:

- The Pacemaker: Past, Present, and Future (2007)
- Cardiac Valves: Past, Present, and Future (2008)
- Minimally Invasive Cardiac Surgery (2009)
- Heart Failure (2010)
- Recent Advances in Cardiac Devices and Procedures (2011)
- Innovations in Cardiovascular Therapy (2012)
- The Evaluation, Management and Long-Term Follow-up of Children with Congenital Heart Disease (2013)
- Advances in Congenital and Adult Heart and Lung Transplantations

25.5 Heart Valves

Initial development in the field of prosthetic heart valves involved the search for biologically compatible materials and hemologically tolerant designs; it is considered today that early successes could not have been achieved without the union of these two factors. At that time, as there was no satisfactory mechanism to scientifically achieve this goal, the trial and error method was used; it is important to note that much of this early work was also performed at the University of Minnesota. The development of prosthetic heart valves

became the purview of several cardiovascular surgeons who often collaborated with engineers. To distinguish one valve from the others, each prosthesis often became identified and named after its surgeon developer [11].

It is notable that Lillehei and his colleagues developed four different valves: (1) a non-tilting disk valve called the Lillehei–Nakib toroidal valve in 1967; (2) two tilting disk valves, the Lillehei–Cruz–Kaster in 1963 and the Lillehei–Kaster in 1970 (produced by Medical Inc. in 1970 and eventually distributed by Medtronic Inc. in 1974); and (3) a bileaflet valve, the Lillehei–Kalke in 1965 (manufactured by Surgitool in 1968 and used clinically by Dr. Lillehei at the New York Cornell Medical Center) (Figs. 25.4 and 25.16).

The St. Jude bileaflet valve was primarily designed by Chris Posis, an industrial engineer who approached Demetre Nicoloff, M.D., a cardiovascular surgeon at the University of Minnesota. This valve had floating hinges located near the central axis of the rigid housing as well as an opening to the outer edge of each leaflet, leaving a small central opening (Figs. 25.4 and 25.17) [12]. Nicoloff first implanted this valve in October 1977, and it provided the foundation for the

beginning of St. Jude Medical as a significant biomedical device company. Dr. Nicoloff was asked to serve as the Medical Director of the new company; however, he declined due to the demands of his clinical practice. Rather, he suggested that Dr. C. W. Lillehei be named as the Medical Director, a post that Lillehei held until his death in 1999 [11].

It is important to note that most of these past valve designs, as well as current designs, were evaluated in animal trials at the University of Minnesota. More specifically, Richard Bianco, Director of Experimental Surgical Services, has been at the University for over 35 years working with a core of clinicians, scientists, and engineers on the design, evaluation, and redesign of their cardiac valves. For more details on such experimental trials, refer to Chap. 27.

More recently, Dr. Robert Wilson, the former Head of Interventional Cardiology at the University of Minnesota, continued this innovative legacy in the field of cardiac heart valves by developing a third-generation approach to a transcatheter aortic valve; he founded Heart Leaflet Technologies, a company that continues to commercialize these devices (www.heartleaflet.com/).

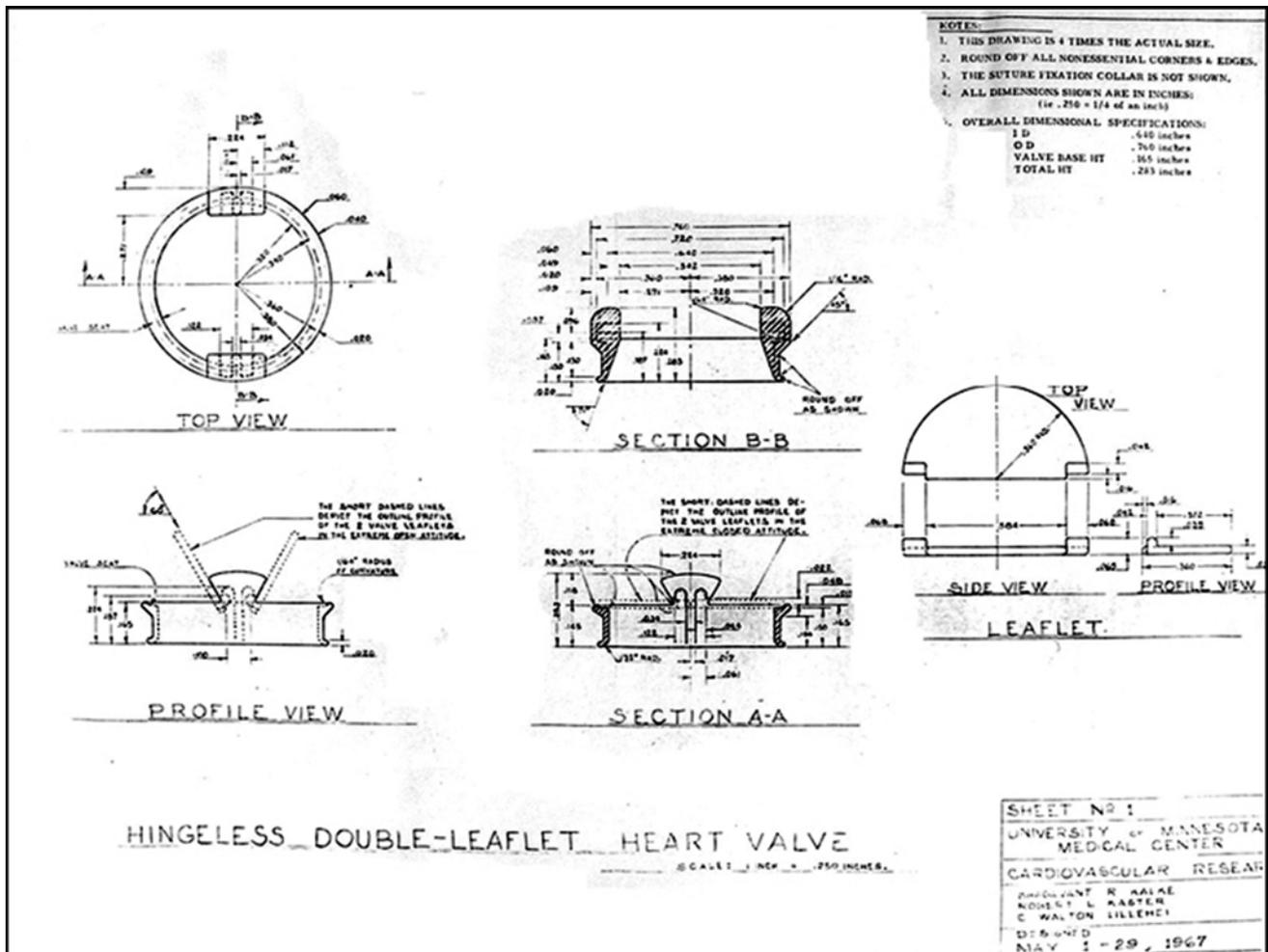


Fig. 25.16 The Lillehei–Kalke rigid bileaflet prosthesis (1968)

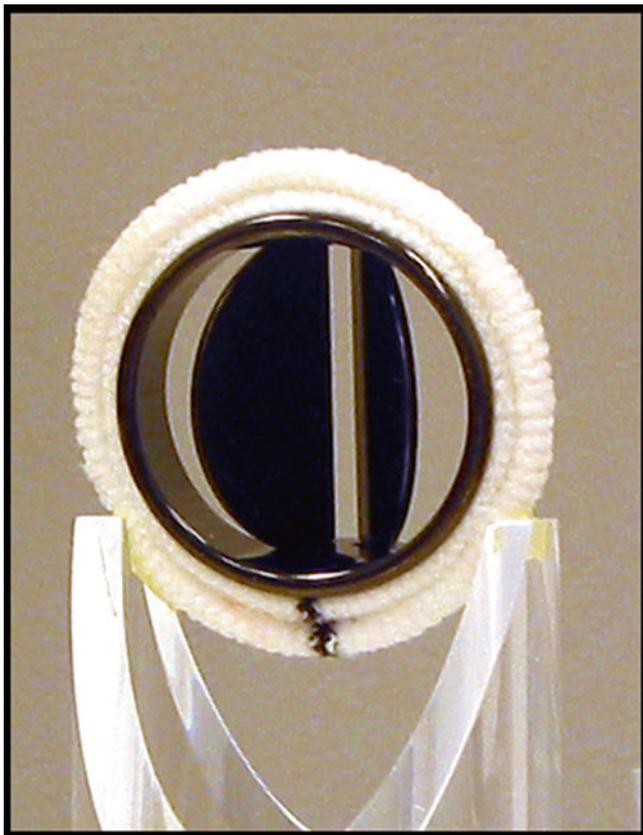


Fig. 25.17 St. Jude bileaflet prosthesis developed in 1976

25.6 Other University-Affiliated Medical Devices

Many of the major breakthroughs in cardiac device development at the University of Minnesota occurred via associated collaborations with the Surgery Department. In more recent times, several more cardiovascular medical devices have been invented in areas other than the Department of Surgery, specifically the Departments of Medicine and Radiology. Examples of such devices and technologies include compression/decompression cardiopulmonary resuscitation devices (Chap. 38) and transcatheter closure devices that are permanent cardiac implants designed to close defects between chambers of the heart (Chap. 37). The later devices are self-expanding, self-centering umbrella-like devices whose design and shape varies, as does the exact mode of their deployment. They are implanted in the heart through catheters inserted into either the artery or vein in a cardiac catheterization laboratory. Transcatheter closure devices are intended to provide a less invasive alternative to open-heart surgery, which has been the standard of care. These closure devices were the brainchild of Dr. Kurt Amplatz, who spent most of his 40-year career in radiology as the Chairman of Interventional Radiology at the University of Minnesota. In

1995, he founded AGA Medical, a publicly held medical technology company that is now a part of St. Jude Medical. Dr. Amplatz also developed many other catheters, guide-wires, etc., and these designs remain as the foundation for numerous technologies still commonly employed today; he is an inventor on 45 US patents.

25.7 Medical Device Regulation

In the 1950s, Earl Bakken adopted the motto of his friend and colleague, Dr. Lillehei, for his initial method of device development—“Ready, Fire, Aim.” In other words, devices were actually tested in humans; therefore, the transition from bench to bedside happened at an accelerated pace [10]. However, in 1976, the Medical Device Amendments to the Federal Food, Drug, and Cosmetic Act established three regulatory classes for medical devices, based upon the degree of control necessary to assure the safety and effectiveness of various types of devices. The most regulated devices are considered class III that, by definition, (1) are devices designed to support or sustain human life, (2) are of substantial importance in preventing impairment of human health, or (3) present a potential unreasonable risk of illness or injury. All devices placed into class III are subject to premarket approval requirements, including a scientific review to ensure their safety and effectiveness.

Under Medical Device Reporting in the FDA, all manufacturers, importers, and user facilities are required to report adverse events and correct them quickly. Although, since 1984, manufacturers and importers of medical devices have been required to report all device-related deaths, serious injuries, and certain malfunctions to the FDA, numerous reports show underreporting. Therefore, the Safe Medical Devices Act (SMDA) of 1990 was implemented; device user facilities must report device-related deaths to the FDA and the manufacturer. In addition, the SMDA requires that device user facilities submit reports to the FDA on an annual basis (FDA Modernization Act of 1998). In the past several years, recalls of defective pacing systems and leads have had a major impact on the medical device industry in the USA, resulting in dramatic shifts within vitally affiliated companies. For more details, refer to Chap. 42.

25.8 LifeScience Alley

Spurred by the flurry of innovations from Minnesota inventors such as the pacemaker, bubble oxygenator, and artificial heart valve, LifeScience Alley (formerly Medical Alley) was established in 1984 as a nonprofit trade association to support the region’s growing healthcare industry [10]. LifeScience Alley was founded by Earl Bakken, founder of

Medtronic Inc.; Bakken, at the current age of 90, remains on the LifeScience Alley Board of Directors to this day as Chairman (Emeritus), and Shaye Mandle currently presides over the association.

In 2010, Dale Wahlstrom (then President and CEO of both LifeScience Alley and the BioBusiness Alliance of Minnesota) led the collaboration between these organizations. Focused on their shared mission to grow and secure Minnesota's position as a global leader in the life sciences, LifeScience Alley now serves nearly 700 member organizations from all sectors of the life science sector, including medical technology and equipment manufacturers, pharmaceutical and biopharmaceutical companies, healthcare providers and insurers, agricultural and industrial biotechnology organizations, academic institutions and government entities, and a broad range of service and consulting companies.

Furthermore, LifeScience Alley hosts a rigorous calendar of events designed to connect, educate, and strengthen the regional life science community including (1) informational programs on the latest industry trends, regulations, and standards; (2) networking events; (3) member updates on trends in employment, capital, and policy issues; and (4) leadership forums and luncheons. Additionally, they host two annual conferences:

1. LifeScience Alley Conference. An event that brings together life science leaders from their diverse member network to discuss trends, promote industry growth, and create valuable connections.
2. MedTech Investing Conference. An event for medical device investors, entrepreneurs, and corporate business development executives to discuss critical issues in the medical device sector and serve as an intimate networking venue to foster the development and financing of companies.

On behalf of its members, LifeScience Alley also develops and supports public policies that promote growth of the life science industry locally, nationally, and globally.

25.9 Design of Medical Device Conference

Since 2001, the University of Minnesota's Medical Device Center, the College of Science and Engineering, the Institute for Engineering in Medicine, and the Academic Health Center have hosted an annual Design of Medical Devices (DMD) Conference every April. This remains today as the largest medical device conference worldwide; its primary goal is to provide an international forum bringing together world-class medical device designers, researchers, manufacturers, and the public sector, to share perspectives and innovations related to medical device design. The conference

further showcases the University of Minnesota as a leader in the medical device community and generates funds from corporate sponsorships to support medical device education at the University. In recent years, the conference has grown to over 1,100 participants annually from 17 different countries and multiple companies and academic institutions [13] (www.dmd.umn.edu).

25.10 The Institute for Engineering in Medicine

The Institute for Engineering in Medicine (IEM) is an interdisciplinary research organization that strives to strengthen collaborative efforts between the disciplines of engineering and biomedicine at the University of Minnesota. Five main themes dominate IEM's focus on research: cardiovascular engineering, neuroengineering, cellular and molecular bioengineering, medical and biological imaging, and medical devices. The IEM mission revolves around creating and applying innovative engineering solutions to medical and health problems, in addition to fostering collaborations with industry. To achieve these goals, IEM sponsors three endowed chairs and a fellowship program, as well as various seminars, workshops, and conferences (Neuromodulation Symposium, Design of Medical Devices Conference, IEM Conference & Retreat). IEM is currently directed by Professor Bin He [14].

25.11 Medical Devices Center

Under the direction of Professor Arthur Erdman, the Medical Devices Center (MDC) was established by the University of Minnesota in 2007 (Fig. 25.4). A primary goal of this center is to strengthen interdisciplinary medical device research among faculty in the Academic Health Center and the College of Science and Engineering. The MDC recently opened a new core facility, which includes (1) a computer-aided design (CAD)/precision instrumentation laboratory with 3D printing, (2) an electronic fabrication laboratory, (3) a mechanical prototyping facility, (4) a testing room—wet laboratory, (5) an anatomy—physiology SimPORTAL laboratory, and (6) a multipurpose room for modeling, assembly, demonstrations, or conferences [15]. The center supports an Innovation Fellows Program to recruit and hire individuals across the medical engineering and clinical disciplines to form cross-functional teams that aim to develop novel medical technologies.

The MDC, in collaboration with Professor Daniel Keefe from the Department of Computer Sciences and various corporate collaborators, has developed a Virtual Prototyping Lab with the goal of simulating the placement of existing or

novel device concept within virtual anatomies (www.mdc.umn.edu/mdc/vrlab). Further support is provided by the Minnesota Supercomputing Institute that provides access to high-performance advanced computational resources and user support to facilitate cutting-edge research in all disciplines, as well as promote technology transfer through the interchange of ideas in the field of supercomputing research. Researchers have ready access to informatics, visualization, and application development services (www.msi.umn.edu).

25.12 Cardiovascular Physiology at the University of Minnesota

The Department of Physiology at the University of Minnesota has a rich history of performing basic cardiovascular research and establishing clinical collaborations within the institution (see Sect. 25.1). Not only have these individuals published many important basic research papers, but they have also been integrally involved in the training of many generations of cardiac physiologists, surgeons, and biomedical engineers.

One of the more notable Chairmen of the Department of Physiology was Maurice Visscher, who was present during the Owen Wangensteen and C. Walton Lillehei eras. In 1936, Dr. Visscher returned to the University of Minnesota to succeed Dean Lyon as the Head of the Department of Physiology (Table 25.4). He first came to Minnesota in 1922 as a graduate student in physiology under the mentorship of Frederick Scott and satisfied the requirements for both Ph.D. and M.D. degrees in a 4-year period of time [16]. Interestingly, subsequent to his studies, Visscher served as a postdoctoral fellow in England at the University College London. While there, he worked under the advisement of the notable cardiac physiologist, Ernest Starling, who, at that time, was near the end of his brilliant career (e.g., Starling's Law of the Heart). Together in 1927, Starling and Visscher published a classic paper in which, using a heart–lung preparation (introduced by Starling in 1910), they reported that the oxygen consumption of the heart was correlated directly with its volume in

diastole, without regard to the amount of work the heart was exerting in pumping blood [17, 18]. After Starling's death in 1927, Visscher continued research on this topic while serving as the Physiology Department Chairman in Minnesota; his research was considered to shed valuable light on the mechanisms underlying heart disease due to coronary occlusion, in general.

It has been described that Owen Wangensteen, having recognized how many of these findings were directly applicable to surgery, initiated collaborations with Visscher and the Physiology Department. To this extent, Wangensteen initiated and conducted a regular Physiology–Surgery Conference that was considered “invaluable in acquainting surgical residents with the techniques of experimental physiology” [18]. Many also credit Wangensteen's academic philosophies for enabling the pioneering advancements in open-heart surgery and subsequent pacemaker technologies at the University of Minnesota. For example, Earl Bakken asked C. Walton Lillehei in 1997, “How did you have the courage to go ahead with these pioneering-type experiments?” Lillehei replied, “As I think, when I look back, that was part of the Wangensteen training system” [19]. He further elaborated, “[Wangensteen] was a unique person in many regards. One [aspect of his] uniqueness was his training system. He had a great faith in research, animal or other types of laboratory research. He felt that the results of his research gave the young investigator the courage to challenge accepted beliefs and go forward, which you would not have had, as I look back, as a young surgical resident. That's why many of the great universities didn't produce much in the way of innovative research, because they were so steeped in tradition. Wangensteen had a wide open mind. If research showed some value, then you should pursue it.”

Importantly, the past few years have brought a renewed interest in refocusing the Physiology Department to again be a leader in the cardiovascular field. In the spirit of Maurice Visscher, the new Department of Integrative Biology and Physiology emerged in recent years under the direction of Professor Joseph Metzger. Departmental research focuses on integrative systems biology of the heart and vasculature, including close linkages among cardiovascular diseases and obesity, diabetes, and metabolism, thus bridging the gap between basic science discovery and clinical application. The department offers a unique intense short course, Advanced Cardiac Physiology and Anatomy, for individuals in industry as well as postdoctoral and graduate students; this course consists of multiple lectures, delivered by clinicians and researchers, related to basic cardiac anatomy, physiology, cardiovascular disease, and clinical diagnosis and treatment, as well as hands-on gross anatomy labs. Further, as a tribute to Maurice Visscher, an annual Visscher Symposium is organized, featuring world-renowned keynote speakers and showcasing graduate student research [20].

Table 25.4 Department of Physiology at the University of Minnesota: chairs/interim heads

Physiology Department chair/interim head	Position	Years served
Richard O. Beard	Department Chair	1889–1913
Elias P. Lyon	Department Chair	1913–1936
Dr. Maurice B. Visscher	Department Chair	1936–1968
Eugene Grim	Department Chair	1968–1986
Richard E. Poppele	Interim Head	1986–1988
Robert F. Miller	Department Chair	1988–1998
Joseph DiSalvo	Interim Head	1998–2002
Douglas Wangensteen	Interim Head	2002–2008
Joseph M. Metzger	Department Chair	2008–present

Dr. Lillehei believed that “What mankind can dream, research and technology can achieve.” And with the support of the Lillehei Heart Institute, in collaboration with the Institute for Engineering in Medicine and other organizations, the circle has been completed.

25.13 Summary

The University of Minnesota has a rich tradition of research and development in the fields of cardiovascular science and medical device design. Today, Minnesota has one of the highest densities of medical device companies in the world, and thus the university remains uniquely positioned to (1) educate the next generation of employees for this industry, (2) be a strong academic collaborator with industry by being an international leader in both basic and clinical cardiovascular research, and (3) serve the additional outreach mission of the university relative to cardiovascular sciences (e.g., partnering with LifeScience Alley and other organizations). The rich legacy of the early pioneers in cardiovascular research, medicine, and surgery lives on at the University of Minnesota.

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Additional Resources

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