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The Lillehei Heart Institute: Building on the Shoulders of Giants

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Abstract Scientific revolutions require a series of paradigm shifts that are promoted by a series of discoveries. These discoveries, paradigm shifts, and scientific revolutions are dependent on timing, environment, and innovative pioneers. More than 50 years ago, a series of discoveries led to such a paradigm shift at the University of Minnesota which in turn revolutionized the field of cardiovascular medicine forever. Today, this spirit of innovation and discovery is alive and thriving at the Lillehei Heart Institute at the University of Minnesota.

Keywords Lillehei Heart Institute · Open Heart Surgery · Cell Therapy · Device Therapy · Cardiovascular Genomics · Cardiovascular Prevention

A History of Cardiovascular Giants

In the 1930s, the University of Minnesota was home to one of the world's first pediatric cardiology programs, which was pioneered by Dr. Paul Dwan. During that period, patients with heart disease primarily had congenital heart disease or suffered from complications of rheumatic heart disease. In support of Dr. Morse Shapiro's treatment of rheumatic heart disease program, the first heart hospital (the Variety Club Heart Hospital at the University of Minnesota) in the world was built which provided an infrastructure unmatched at any other institution [1]. The 80 bed Variety Club Heart hospital included a 40-bed adult cardiology unit, a 40-bed pediatric cardiology unit, a cardiac catheterization laboratory, outpatient clinics, and an auditorium and opened its doors on March 18, 1951 (Fig. 1). In addition to this cardiovascular infrastructure, visionary leadership was provided by Dr. Owen H. Wangensteen, the chairman of the Department of Surgery at the University of Minnesota, who engineered an innovative, academic program for cardiovascular specialists [1, 2]. While Wangensteen was a general surgeon who did not perform cardiac surgery, he emphasized that his trainees and faculty have a strong foundation in basic science and experimentation in the laboratory. A frequent quote of his was "Don't think, do the experiment". Importantly, it was Wangensteen's insistence on laboratory science for his clinical faculty and his unwavering support of his faculty to challenge the long held beliefs and dogma that had limited progress and the treatment of diseases such as heart disease [1, 2]. These two sparks, a state of the art heart hospital and visionary leadership, ignited the technological revolution at the University of Minnesota that changed the world.

Champions that Led the World

In the post-World War II era, a number of surgeons returned to the University of Minnesota to complete their training and assume faculty positions. At that time, surgical interventions consisted of closed heart surgical procedures as no one believed that open heart surgery was possible. On September 2, 1952, University of Minnesota Surgeons, F. John Lewis assisted by Richard Varco and second assistant, C. Walton Lillehei, performed the first successful open heart surgical procedure in the world to close an atrial septal defect (ASD) in a 4-year old patient (Fig. 1) [1]. This procedure was accomplished using hypothermia (a cooling blanket) to

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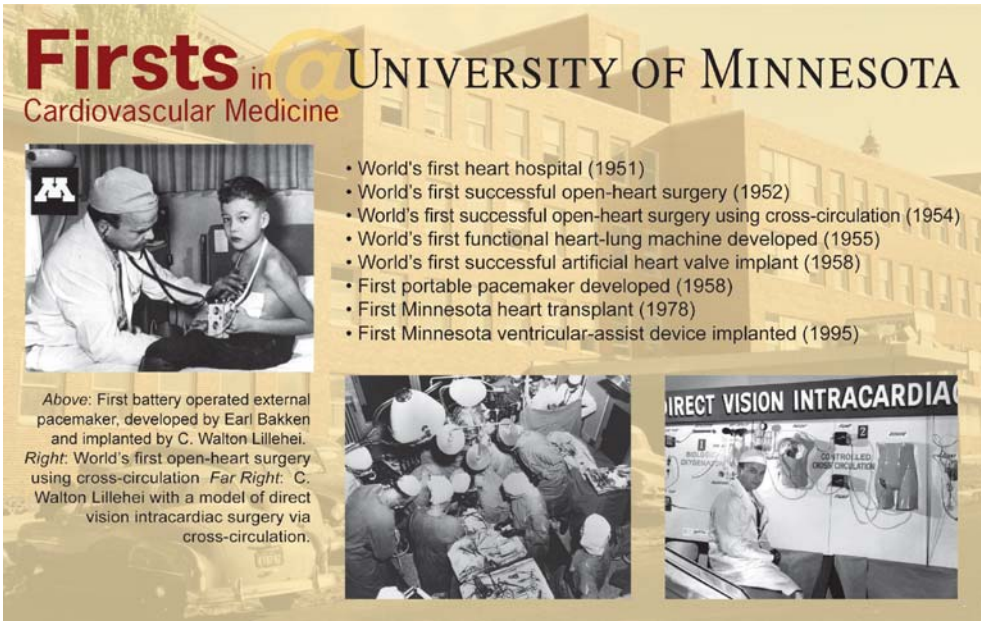

Fig. 1 Pioneering cardiovascular initiatives at the University of Minnesota. *Background image* is that of the world's first heart hospital in 1951, the Variety Club Heart Hospital at the University of Minnesota. All images were obtained from the University of Minnesota archives

lower the body temperature to 82°F for the 10-min surgical procedure, which was followed by the rewarming of the body using a water bath. In total, Dr. F. John Lewis performed more than 50 ASD closures using the hypothermic method over a 3-year period at the University of Minnesota [1]. These monumental procedures provided a platform for revolutionary initiatives directed by C. Walton Lillehei. Within 18 months of the world's first successful open heart surgical procedure at the University of Minnesota, Dr. Walt Lillehei (assisted by Drs. Morley Cohen, Richard Varco, and Herbert Warden) performed the first successful open heart surgical procedure using cross circulation in the world (closure of a ventricular septal defect; VSD) on March 26, 1954 (Fig. 1) [1]. The patient was 13-month-old Gregory Glidden and the biological oxygenator was his father. This procedure required an ABO compatible family member (typically a parent) to serve as a human oxygenator as blood bypassed the heart of the patient and was oxygenated by the donor. Despite its success and innovative advance, cross circulation was controversial as some stated that the mortality of the procedure could be as high as 200% (if both patient and the oxygenator were to die) [1–4]. Importantly, Wangensteen provided the essential support necessary for his surgeons to pursue these innovative procedures in a patient population that otherwise had limited life expectancy with conventional medical therapy [1]. With this support over the following 2-year period (1954–1955), Lillehei utilized cross circulation in 45 patients without donor (i.e., biological oxygenator) mortality [3]. Using cross circulation, Lillehei performed the world's first successful closure of a VSD, the first atrioventricular canal repair and the first tetrology of Fallot repair in children with congenital heart disease [1, 3]. Importantly, this seminal advance (i.e., cross circulation) by Lillehei led to a number of further innovative procedures. One of these procedures was the use of the heterologous lung preparation in an attempt to provide a non-human oxygenator for the patient. In total, seven patients at the University of Minnesota utilized this strategy that included canine lungs as oxygenators. One of these patients survived. All of these initiatives required experimentation, which was undertaken in Lillehei's laboratory within Dr. Maurice Visscher's Physiology Department. Parenthetically, the scientific environment within the Physiology Department at the University of Minnesota provided Lillehei with a number of collaborative interactions that proved to have direct clinical applications. While the use of cross circulation and heterologous lungs were not widely used, they proved to be an essential intermediate step to the development and wide use of the oxygenator [1].

One of these initiatives was the development of the helical bubble oxygenator. Dr. Richard DeWall, a surgical fellow, worked in Lillehei's laboratory and focused on the design of a bubble oxygenator which was widely held to be too risky due, in part, to the risk of air embolism. Over a 2-year period, refinements led to the design of the DeWall-Lillehei bubble oxygenator that was designed to be inexpensive, disposable, and lacked any moving parts [4]. On May 13, 1955, Lillehei utilized the DeWall-Lillehei oxygenator as the first successful heart–lung machine, which ultimately became the machine of choice worldwide for open heart surgical procedures [4].

Further innovative initiatives by Lillehei resulted in the placement of the first battery-operated transistorized pacemaker which was undertaken in collaboration with Earl Bakken (co-founder of Medtronics, Inc.; Fig. 1), the

world's first mitral valve repair and the design of artificial heart valves (the Lillehei-Nakib toroidal disk valve in 1966; the Lillehei-Kaster tilting disk valve in 1967; and the Kalke-Lillehei rigid bileaflet valve in 1968) [1, 2]. Importantly, these collaborations between Lillehei, University of Minnesota faculty, and engineers within the community helped establish a rich biomedical Minnesota Industry, which in its own right have revolutionized cardiovascular medicine through the production of heart valves, pacemakers, ICDs, and other technologies, which have decreased the morbidity and mortality for patients with heart disease.

Through these titanic advances, the University of Minnesota was a magnet for cardiovascular surgical and medical training opportunities [1, 5]. The list of specialists having received training and advanced degrees under Lillehei are a Who's Who in Cardiovascular Medicine numbering more than 150 cardiovascular surgeons including Drs. Christian Barnard (performed the first heart transplant in the world), Aldo Castañeda (Surgeon-in-Chief at the Children's Hospital Boston, Harvard Medical School), Morley Cohen (performed the first open heart surgery in Manitoba in 1959), Richard DeWall (co-designer of the DeWall-Lillehei oxygenator), Vincent Gott (Chair of Surgery at Johns Hopkins), Norman Shumway (regarded as the father of heart transplantation), and Herbert Warden (performed the first open heart surgical procedure in West Virginia) [5].

Lillehei is regarded as the father of open heart surgery and his impact is reflected in the more than one million open heart surgical procedures performed worldwide each year. In addition, he received a number of honors that total more than 80 including the Lasker Award (awarded in 1955) and the Harvey Prize in Science and Technology, and he was nominated seven times for the Nobel Prize [1, 2]. He and his colleagues remain giants on whose shoulders we stand to further revolutionize and innovate new therapies for patients with heart disease at the University of Minnesota.

Cardiovascular Medical Advances

As the second director of the cardiovascular program, Dr. Jay N. Cohn (1974–1996) instilled a culture of experimentation through basic science and clinical trials. Often referred to as the "Father of Vasodilator Therapy", Dr. Cohn directed a number of seminal trials that established the role of vasodilator agents and improved survival of patients with heart failure [6]. He also discovered the role of nitric oxide to slow progression of heart disease and more recently developed screening strategies to identify patients at risk for an adverse cardiovascular event. Cohn was the founder and inaugural president of the Heart Failure Society of America and Editor-in-Chief of the Journal of Cardiac Failure. Cohn too influenced a generation of clinician-scientists and established arguably the premier heart failure program in the country at the University of Minnesota.

The Lillehei Heart Institute

The Lillehei Heart Institute was established in 1999 through the philanthropic support of Kaye Lillehei, wife of the late Dr. C. Walton Lillehei. This institute has continued to propagate the pioneering spirit of C. Walton Lillehei and serves as the center for innovation, discovery, and experimentation. Today, the University of Minnesota leads the world in the use of technologies for the treatment of advanced heart disease. In partnership with the state of Minnesota, the University of Minnesota has allocated funds to build a new heart building that will be home to the Lillehei Heart Institute. Strategic faculty retentions and faculty recruitments have established a world class program in advanced heart failure management, mechanical support, orthotopic heart transplantation, and emerging technologies for the prevention, diagnosis, and treatment of heart disease.

Pioneering Initiatives at the LHI

Stem Cell Biology and Cell Therapy for Heart Disease The University of Minnesota is regarded as one of the premier stem cell institutions in the world. Following the world's first successful bone marrow transplantation by Dr. Robert Good at the University of Minnesota (1967), this institution has continued to lead the world in bone marrow transplantation. Such an environment has promoted studies by LHI investigators that have led to the identification of cardiac stem cell populations that are resident in the developing and adult heart. Moreover, studies are in progress to decipher the molecular circuits that govern these stem cell populations to enhance their proliferative capacity and their plasticity [7]. Further, translational applications are underway to deliver autologous cardiac stem cells in the patient population that are supported with a left ventricular assist device. These clinical trials are designed to mechanistically examine the capacity of stem cell populations to participate in the repair and regeneration of the failing heart. The discoveries are also complemented by innovations designed to rebuild the decellularized heart (undertaken in the Center for Cardiac Repair at the University of Minnesota; Doris Taylor, Ph.D., Director) [8]. These strategies further allow University of Minnesota investigators to examine the ability of somatic stem cell populations to generate cardiac lineages, repopulate the decellularized heart, and form a

functional electrically coupled syncytium. Importantly, the University of Minnesota is the only institution that has membership in both the NHLBI CV Cell Therapy Research Network and the NHLBI Clinical Heart Failure Research Network that promotes the investigation of emerging therapeutic applications at the UMN in trials conducted across the USA.

Device Therapies for Heart Disease Advances in device development for cardiovascular diseases continue to be undertaken to develop improved high resolution mapping of arrhythmogenic cardiac foci, more durable mechanical heart (ventricular) pumps [9], artificial valves that can be delivered percutaneously, and ASD/VSD percutaneous closure devices. Moreover, heart failure specialists at the University of Minnesota are utilizing ultrafiltration and robotic surgical procedures to treat patients with advanced cardiovascular disease [9, 10]. These collaborative efforts (see below) provide a synergy for innovation and discovery for new therapies for heart disease at the University of Minnesota.

Cardiovascular Prevention and Genomics The effort to prevent cardiovascular disease in addition to the treatment of advanced disease has emerged as a major challenge. Identifying those in need of treatment has heretofore been based on the so-called risk factor assessment which is neither sensitive nor specific in identifying those with disease. The Cardiovascular Prevention Center (Directed by Dr. Jay Cohn) at the University of Minnesota (within the LHI) has introduced a screening process in which non-invasive testing is utilized to identify early abnormalities of the blood vessels or heart that place patients at high risk for progression of disease that can be prevented by treatment. Early experience indicates that this approach is far more sensitive than the traditional risk factor assessment in predicting future morbid events. Indeed, appropriate screening of asymptomatic adults and treatment of individuals with early abnormalities could eventually eliminate heart attacks, heart failure, and strokes in our productive population.

The LHI Cardiovascular Genomics Program (Directed by Dr. Jennifer Hall) collaborates with the Cardiovascular Disease Preventive Program to examine or identify signatures of gene expression that increases the susceptibility of patients for heart disease (hypertension, heart attacks, heart failure, etc.) [10]. Broadly, this strategy is referred to as personalized medicine. These strategies allow us to monitor patients over time in the Prevention Program, and based on their changes in gene expression, our goal is to intervene (prior to the onset of disease) with medical therapies to arrest the onset or progression of cardiovascular disease. We believe that these molecular technologies will revolutionize our approach to cardiovascular health and the treatment of disease (from the treatment of end stage disease to the arrest of cardiovascular diseases). This would dramatically change the way in which medicine is currently practiced. This, in turn, will allow the investigators to enhance their understanding of the cause of heart disease, identify early biomarkers, and develop strategies to slow or arrest the progression of the disease.

Women's Cardiovascular Health Program The LHI Women's Heart Program was formed in 2005, following the designation by the Department of Health and Human Services as a Center of Excellence in Women's Health. Patients come specifically referred by other physicians or as self-referrals to this clinic because of the publicity which has educated women about their unique risks and outcomes with heart disease. The Women's Program is now a nationally recognized program and grants have been obtained from a number of agencies. The program received a Center of Excellence in Women's Health award from the D.H.S.S., and it was awarded a partnership in the National Institutes of Health Heart Truth professional education campaign which allowed the program to partner with the Rural Physician Associate Program to bring presentations to out-state Minnesota Area Health NorthPoint Community Center of Excellence, the Minnesota Area Health Education Center, and with the Center for American Indian and Minority Health, located in Duluth, MN. Initiatives for this program center on the education of and treatment of patients; research to decipher the gender-specific risks for cardiovascular disease, the gender-specific biomarkers, and signatures of gene expression in women susceptible to cardiovascular disease; and the education of fellows regarding gender-specific risks for cardiovascular disease.

Educating Future Generations of Cardiovascular Specialists

An important goal associated with our mission is to train the future generation of physicians for careers in cardiovascular medicine, science, and innovation. The University of Minnesota Cardiology Program was the first cardiovascular fellowship program in the state of Minnesota (established in 1961). In total, we have trained more than 300 cardiologists that have contributed and established an improved cardiovascular healthcare program throughout Minnesota. The fellowship program provides a year of dedicated research time to pursue research projects of interest in collaboration with their mentors. Formal programs have been established for fellows to pursue doctoral degrees in Physiology, advanced training in a combined CV-Medical Device Design fellowship, a masters of public health degree from the world class UMN School of Public

Health, and a clinical/clinical research exchange program with Bangalore Hospital in India. The goal of these training opportunities is to provide an environment, in combination with mentors, to help trainees to reach their full potential—to foster the lifelong pursuit of learning and knowledge.

Strategic Partnerships Provide Unlimited Potential for Paradigm Shifts

The LHI has benefited from the array of collaborative programs at the University of Minnesota. Among these programs, collaborations have been established between the LHI and the cardiac surgical program (Dr. Herb Ward), the Center for Cardiac Repair (directed by Dr. Doris Taylor), the Biomedical Engineering Institute (directed by Dr. Jeff McCullough), the Experimental Surgical Program (directed by Richard Bianco), the Department of Integrative Physiology (Joseph Metzger, Ph.D., Chairman), the Center for Developmental Biology (Scott Selleck, M.D., Ph.D., Center Director), the Stem Cell Institute (Jonathan Slack, Ph.D., Center Director), Center for Translational Medicine (Bruce Blazar, M.D., Center Director; John Wagner, M.D., Co-Director), and The Paul and Sheila Wellstone Muscular Dystrophy Center (John Day, M.D., Ph.D., Director) among others. Moreover, the opportunity to collaborate and form partnerships with neighboring industries (Medtronic Inc., St. Jude Medical, Inc., 3M Co., Boston Scientific, Corp., etc.) in the state of Minnesota further allows for significant advances for emerging technologies for patients with heart disease.

In 2002, yet another strategic partnership was established between the University of Minnesota and the Mayo Clinic to form the Minnesota Partnership for Biotechnology and Medical Genomics. This partnership has resulted in a number of cardiovascular accomplishments, joint peer-reviewed publications, successful grant applications, and patents. As in the early 1950s, the University of Minnesota today has established a one-of-a-kind multidisciplinary cardiovascular program focused on innovation.

In summary, the University of Minnesota has an established reputation for innovation and excellence in cardiovascular medicine. New investments in the form of a new heart building, strategic partnerships, and an environment to support visionary pioneers position the Lillehei Heart Institute to lead in the areas of basic science, translational clinical trials, patient care, and education to revolutionize the understanding and treatment of heart disease.

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