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The Journal of Heart and Lung Transplantation: 50 years of heart transplantation progress

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The world's first human heart transplant was performed at Groote Schuur Hospital in Cape Town by the South African surgeon, Christiaan Barnard. This is the first photograph of the surgical team taken on the afternoon of Sunday, December 3, 1967. Credit: David K.C. Cooper

This month marks the 50th anniversary of the world's firrst human heart transplant performed at Groote Schuur Hospital in Cape Town by South African surgeon, Christiaan Barnard. He transplanted the heart of a 25-year-old woman into Louis Washkansky, a 53-year-old diabetes patient who was in severe heart failure. Today, over 5,000 heart transplants are performed each year globally, more than half of which are in the US. A special issue of *The Journal of Heart and Lung Transplantation* presents a chronicle of the major milestones in heart transplantation over the last 50 years.

Editor-in-Chief of the journal, Mandeep R. Mehra, MD, FACC, FESC, FHFSA, FRCP, Brigham Health Center for Advanced Heart Disease and Harvard Medical School, comments that, "This 50-year journey has established heart transplantation as a pivotal life-extending choice in patients with advanced heart failure; yet, challenges remain with complications of immunosuppression and late complications limiting survival. The near future offers great hope in expanding the donor pool through use of donation after circulation death (DCD), new donor sources such as xenotransplantation, and competing technology such as artificial hearts and tissue regeneration."

Since 1967, more than 150,000 patients worldwide have benefited from heart transplantation, returning a nearly normal quality of life to those with end-stage heart failure while extending life by a median of 14 years. This issue presents ten editorials by the top experts in the field that highlight the evolution of heart transplantation and honor the pioneers responsible for these ground-breaking achievements.

It was the dream of many cardiac surgeons in the mid-20th century to transplant a healthy heart into a patient dying of end-stage heart disease. The technique Barnard used was established by Norman Shumway and colleagues at Stanford, and originally described by Russell Brock in London. Although Barnard's first patient died after 18 days, his second

patient, Philip Blaiberg, lived a full and relatively active life for 19 months. His fifth and sixth patients lived for 12 and 23 years, respectively.

Barnard's successes and the pioneering operations of Norman Shumway and Richard Lower in the US kept alive the hope that heart transplantation would eventually become a routine form of treatment. David K.C. Cooper, MD, PhD, of the Xenotransplantation Program, Department of Surgery, University of Alabama at Birmingham, and Barnard's biographer, was a surgical colleague of Barnard for several years in South Africa and later in the US. In the issue's opening article, he writes, "Today, when heart transplantation has become a relatively routine and commonplace procedure, we may be inclined to underestimate Barnard's immense con?dence and courage in undertaking this ?rst operation. By any standard, it was a monumental step to take."

The first human heart transplantations in the US were performed by Norman Shumway and Edward B. Stinson in January 1968, and by Shumway's research fellow Richard Lower four months later. The results were disappointing. There were 150 transplants worldwide during 1968 and 1969 performed by 50 different teams with universally poor outcomes. Early cases showed the need for better technology for diagnosing rejection, better availability of donor hearts, and a better technique for recovering the donor heart short of waiting for cessation of electrical activity. The procedure became quite contentious, and in 1970 there was an unofficial moratorium on human heart transplantation.

In their article "Conquering the First Hurdles in Cardiac Transplantation: In the Footprints of Giants," Michael L. Hess, MD, formerly medical director of the cardiac transplantation program at the Medical College of Virginia, and Sharon Hunt, MD, medical director of the Stanford University program, explain the challenges facing the early heart transplant surgeons. They summarize the research advances leading up to

the introduction of the new immunosuppressive agent cyclosporine in the early 1980s, which had been used successfully in the related field of renal transplantation. Other advances included validation of the endomyocardial biopsy to diagnose graft rejection and document its resolution after therapy, as well as validation of safe cold preservation of donor hearts to permit distant heart procurement and societal and legal acceptance of a definition of brain death.

"Thus, it was the dedicated initial giants of the field that broke the barriers to successful cardiac transplantation. The early research of Shumway and Lower, the first human case by Barnard, the development of successful cold organ storage allowing long distance transport, and the refinement of immunosuppressant protocols. All these culminated in the institution of the formal disciplines of cardiac transplant surgery and transplant cardiology and the formation of our society which has truly pioneered the rapid expansion in our field," write Hess and Hunt, who respectively worked with Lower and Shumway.

In his article "The Dark Early Years of Heart Transplantation: Some Lessons Learned," Sir Terence English, KBE FRCS FRCP, who was Consultant Cardiothoracic Surgeon at the Papworth Hospital and Addenbrooke's Hospital, Cambridge, UK from 1973-1995, describes the early years in the UK. Sir Terence led the team that performed the first successful heart transplant at Papworth in 1979 and went on to head up one of Europe's most successful heart-lung transplant programs. After the lifting of the moratorium on heart transplants and the introduction of a cyclosporine-based regime in 1982, the team reported an 80% one-year survival for the next 45 patients. By September 2017 Papworth had 15 patients who had either lived or were living more than 30 years after heart transplantation, the longest being three months short of 35 years. "This is something that I could never have imagined when we started our program 38 years ago," he writes.

The first bridge-to-transplant operation was performed in 1969 by Denton Cooley, MD, founder of the Texas Heart Institute, using a mechanical total arti?cial heart. From 1972 on efforts were directed towards long-term mechanical assist and replacement devices. O.H. Frazier, MD, of the Texas Heart Institute, Houston, provides perspective on how this evolved. "The introduction of cyclosporine dramatically expanded the use of heart transplantation and made bridging patients to transplant feasible," he explains. "It was also the single most important contribution to the advancement of mechanical cardiac support from animal experimentation to meaningful clinical application."

The ?rst multicenter immunosuppression trial was reported in early 1998. This study was pivotal in making mycophenolate mofetil (MMF) the antimetabolite of choice in heart transplantation. Jon Kobashigawa, MD, of the Cedars-Sinai Heart Institute, Los Angeles, provides an overview of this and other clinical trials that shaped immunosuppression use in heart transplant medicine. "There is a ?ne balance between the numerous risks of life-long immunosuppression and the risk of rejection. As new agents are discovered, clinical trials will continue to guide clinicians and bene?t patients," he writes.

An accelerated form of atherosclerosis, now recognized as cardiac allograft vasculopathy, was first seen in the transplanted heart of the second transplant patient at Grote Schuur. "The advent of intravascular ultrasonography in the early 1990s allowed for an inside look early on in the transplant process to improve our understanding of this disease," explains Dr. Mehra. "However, we need a concerted strategy to decrease early immunologic events that initiate the inflammatory cascade and simultaneously to address the non-immune and inflammatory pathways that are responsible for propagation of the disease. Only then will long-term survival for cardiac transplantation be manifest, and I am hopeful that in 50 years, when this summary will be updated, that these ideas will have been entrenched in more focused and individualized therapy for

cardiac allograft maintenance."

In the 1980s a debate on Medicare coverage of heart transplantation led to the establishment of the National Heart Transplantation Study (NHTS), designed to consider the patient selection process, the long-term social, economic, and ethical consequences of the procedure, and the potential for national expansion of the heart transplantation procedure. This had broad implications for insurance coverage of heart transplantation in the US. A once-experimental procedure had become standard therapy for end stage heart disease. "What started off as a narrow decision related to Medicare coverage of heart transplantation ultimately became the basis for what proved to be an extensive technology assessment," writes Roger W. Evans, PhD, of the United Network for the Recruitment of Transplantation Professionals, Rochester, MN, who was the project director.

Joren C. Madsen, MD, DPhil, of the Center for Transplantation Sciences and Division of Cardiac Surgery, Department of Surgery, Massachusetts General Hospital, reviews the advances, or lack thereof, made in understanding the alloimmune response, immunosuppression, tolerance and xenotransplantation. Madsen predicts that advances such as xenotransplantation (transplantation of animal organs from one species into another) may be creatively integrated with advances in other emerging technologies, such as genome editing, synthetic biology, and bioengineering, in the next 50 years. "The result will be novel therapies that will combine with heart transplantation (or even replace transplantation) to provide a normal and productive life for all patients with end-stage heart disease," he concludes.

Kathleen L. Grady, PhD, MS, RN, Northwestern University Chicago, discovered a passion for understanding the quality of life of advanced heart failure patients treated with surgical therapies while nursing in the early 1970s. She chronicles the changes and developments in nursing

care of heart transplant and mechanically-assisted patients and health-related quality of life (HRQOL), as transplantation and technology evolve. "It is incumbent upon us to base our practice on scientifically rigorous research, so that clinical care of these challenging patients, including shared decision making, self-care, adherence to the medical regimen, and enhancing HRQOL is grounded in evidence," she writes.

In 1991, Hamilton Naki retired from his position as a surgical laboratory assistant after 37 years of service to the profession of transplant surgery at the University of Cape Town. Despite his humble beginnings and the oppressive apartheid regime under which he lived for most of his life, he was honored with a Master of Science in Medicine degree by the University of Cape Town in 2003. Liesl Zühlke, MBChB, PhD, Department of Child and Adolescent Health, University of Cape Town, and Bongani M. Mayosi, DPhil, head of the Department of Medicine at Groote Schuur Hospital and University of Cape Town, recount the story of how Naki became assistant, then anesthetist for the animals, and finally principal surgical assistant in the laboratory of Robert Goetz, Professor of Surgery, and later Christiaan Barnard, assisting in the training of scores of surgeons from all over the world who passed through the transplant unit. "Barnard described him as having incredible dexterity and finesse and is quoted as saying 'If Hamilton had had the opportunity to study, he would probably have become a brilliant surgeon,'" they write. The Hamilton Naki Clinical Scholarship was established in 2007 on the 40th anniversary of the first heart transplant.

In 2015, surgeons in Cambridge, UK achieved a significant advancement in the transplantation of non-beating hearts. In a Special Feature article, this team led by Consultant Surgeon Stephen R. Large, MS, FRCS, FRCP, reports the findings from a study comparing outcomes of donation after circulation death (DCD) heart transplantation against matched donation after brain death (DBD) heart transplants. Building on work previously done by teams in Denver, Colorado and Sydney,

Australia, this is the largest single-center experience. Survival at 90 days was not significantly different between the two groups. However, the team acknowledges that the longer-term results are unknown. "The effects of prolonged warm ischemia and machine perfusion on the coronary endothelium and the development of cardiac allograft vasculopathy have yet to be determined," says Large.

"The pioneering activities by the team should be lauded and the entire team complimented for pursuing this inventive work, yet many issues will need to be considered as further work in this arena is entertained," comments Dr. Mehra in an accompanying editorial. "Perhaps one of the greatest challenges will be in scaling the technology across continents and geographic regions. This is so because the definitions of circulatory death vary greatly and the local tolerance for such a donor source is not consistent."

More information: The articles are:

"Life's defining moment: Christiaan Barnard and the first human heart transplant," by David K.C. Cooper, MD, PhD (dx.doi.org/10.1016/j.healun.2017.10.001)

"Conquering the First Hurdles in Cardiac Transplantation: In the Footprints of Giants," by Michael L. Hess, MD, and Sharon Hunt, MD (dx.doi.org/10.1016/j.healun.2017.10.007)

"The Dark Early Years of Heart Transplantation: Some Lessons Learned," by Sir Terence English KBE FRCS FRCP (dx.doi.org/10.1016/j.healun.2017.10.005)

"Evolutionary perspective of mechanical circulatory support as a bridge to heart transplantation," by O.H. Frazier, MD (dx.doi.org/10.1016/j.healun.2017.10.002)

"Clinical trials in heart transplantation: The evolution of evidence in immunosuppression," by Jon Kobashigawa, MD (dx.doi.org/10.1016/j.healun.2017.10.009)

"The scourge and enigmatic journey of cardiac allograft vasculopathy," by Mandeep R. Mehra, MD (dx.doi.org/10.1016/j.healun.2017.10.010)

"Insurance coverage of heart transplantation in the United States: The dilemma, the debate and the definitive decision that ultimately determined the future of transplantation," by Roger W. Evans, PhD (dx.doi.org/10.1016/j.healun.2017.10.004)

"Advances in the immunology of heart transplantation," by Joren C. Madsen, MD, DPhil (dx.doi.org/10.1016/j.healun.2017.10.003)

"The Role of Nurses In Understanding and Enhancing Quality of Life: A Journey from Heart Transplantation to Advanced Heart Failure," by Kathleen L. Grady, PhD, MS, RN (dx.doi.org/10.1016/j.healun.2017.10.008)

"The Life and the Legacy of Hamilton Naki : Experimental Heart Transplant Surgeon and Teacher," by Liesl Zühlke and Bongani M. Mayosi (dx.doi.org/10.1016/j.healun.2017.10.006)

"Outcome after heart transplantation from donation after circulatory-determined death donors," by Simon Messer, Aravinda Page, Richard Axell, Marius Berman, Jules Hernández-Sánchez, Simon Colah, Barbora Parizkova, Kamen Valchanov, John Dunning, Evgeny Pavlushkov, Sendhil K. Balasubramanian, Jayan Parameshwar, Yasir Abu Omar, Martin Goddard, Stephen Pettit, Clive Lewis, Anna Kydd, David Jenkins, Christopher J. Watson, Catherine Sudarshan, Pedro Catarino, Marie Findlay, Ayyaz Ali, Steven Tsui, and Stephen R .Large (dx.doi.org/10.1016/j.healun.2017.10.021)

"Editorial: Challenges, diligence, and a breakthrough in donation after circulatory death in heart transplantation," by Mandeep R. Mehra, MD (dx.doi.org/10.1016/j.healun.2017.10.022)

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