Includes interactive eBook with complete content

Cardiopulmonary Bypass and Mechanical Support

PRINCIPLES AND PRACTICE

FOURTH EDITION

Glenn P. Gravlee
Richard F. Davis
John W. Hammon
Barry D. Kussman

Wolters Kluwer

Editors

Glenn P. Gravlee MD
Professor
Vice Chair for Faculty Affairs
Department of Anesthesiology
University of Colorado School of Medicine
Anschutz Medical Campus
Aurora, Colorado

Richard F. Davis MD, MBA
Affiliate Professor of Anesthesiology (Retired)
Department of Anesthesiology and Perioperative Medicine
Oregon Health and Science University
Portland, Oregon

John W. Hammon MD
Professor of Surgery, Emeritus
Department of Cardiothoracic Surgery
Wake Forest University School of Medicine
Winston-Salem, North Carolina

Barry D. Kussman MBBCh, FFA(SA)
Associate Professor of Anaesthesia
Harvard Medical School
Senior Associate in Cardiac Anesthesia
Department of Anesthesiology, Perioperative & Pain Medicine
Boston Children's Hospital
Boston, Massachusetts

Contributors List

Darryl Abrams, MD
Assistant Professor of Medicine
Division of Pulmonary, Allergy, and Critical Care
Columbia University Medical Center
New York, New York

Iki Adachi, MD
Associated Surgeon, Co-Director of Mechanical Circulatory Support
Congenital Heart Surgery, Texas Children's Hospital
Assistant Professor
Department of Surgery and Pediatrics
Baylor College of Medicine
Houston, Texas

Sarah K. Armour, MD

Assistant Professor
Department of Anesthesiology
Mayo Clinic
Rochester, Minnesota

Frank A. Baciewicz Jr., MD
Professor Cardiothoracic Surgery, Chief
Division of Cardiothoracic Surgery
Wayne State University
Chief, Thoracic Surgery
Karmanos Cancer Center
Detroit, Michigan

Karsten Bartels, MD
Assistant Professor of Anesthesiology and Surgery
University of Colorado School of Medicine
Anschutz Medical Campus
Aurora, Colorado

Daniel Brodie, MD
Associate Professor of Medicine
Department of Medicine
Columbia University College of Physicians and Surgeons
New York, New York

John F. Butterworth IV, MD
Professor and Chairman
Department of Anesthesiology
Virginia Commonwealth University Health System
Richmond, Virginia

Paul J. Chai, MD
Congenital and Pediatric Cardiac Surgery
Morgan Stanley Children's Hospital of NY
Columbia University Medical Center
New York, New York

W. Randolph Chitwood Jr., MD, FACS, FRCS (England)
Emeritus Professor and Chairman
Department of Surgery, Founder
East Carolina Heart Institute, East Carolina University, Vidant Medical Center
Greenville, North Carolina

Joseph C. Cleveland Jr., MD
Professor of Surgery

Surgical Director Cardiac Transplantation and Mechanical
Circulatory Support
University of Colorado School of Medicine
Anschutz Medical Center
Aurora, Colorado

Mark E. Comunale, MD
Professor of Anesthesiology
Loma Linda University School of Medicine
Chief Medical Officer for Patient Safety, Associate Medical Director for Perioperative Services and Chairman
Department of Anesthesiology
Arrowhead Regional Medical Center
Colton, California

Vincent R. Conti, MD, FACS
Professor and Chief Cardiothoracic Surgery
University of Texas Medical Branch
Galveston, Texas

David J. Cook, MD
Professor
Department of Anesthesiology
Mayo Clinic College of Medicine
Rochester, Minnesota

John R. Cooper Jr., MD
Attending Anesthesiologist
Department of Cardiovascular Anesthesia
Texas Heart Institute
Clinical Professor of Anesthesiology
Baylor College of Medicine
Houston, Texas

Joseph S. Coselli, MD
Professor and Chief of the Division of Cardiothoracic Surgery
Michael E. DeBakey, Department of Surgery
Baylor College of Medicine, and Chief of the Section of Adult Cardiac Surgery
The Texas Heart Institute
Houston, Texas

Terry N. Crane, BS, CCP, LP
Director
Texas Heart Institute School of Perfusion
Houston, Texas

Laurie K. Davies, MD

Associate Professor of Anesthesiology & Surgery
University of Florida
Gainesville, Florida

Richard F. Davis, MD, MBA
Affiliate Professor of Anesthesiology (Retired)
Department of Anesthesiology and Perioperative Medicine
Oregon Health & Science University
Portland, Oregon

Anthony de la Cruz, MD
Assistant Professor
Department of Anesthesiology
Rush University Medical Center
Chicago, Illinois

Kim I. de la Cruz, MD
Assistant Professor
Division of Cardiothoracic Surgery
Michael E. DeBakey Department of Surgery
Attending Surgeon
Department of Thoracic & Cardiovascular Surgery
Texas Heart Institute
Baylor St. Luke's Medical Center, CHI St. Luke's Health System
Houston, Texas

James A. DiNardo, MD
Professor of Anaesthesia
Harvard Medical School
Chief
Division of Cardiac Anesthesia
Francis X. McGowan Jr., MD Chair in Cardiac Anesthesia
Boston Children's Hospital
Boston, Massachusetts

Alan Finley, MD, FASE
Associate Professor
Anesthesia and Perioperative Medicine
Medical University of South Carolina
Charleston, South Carolina

Charles D. Fraser Jr., MD
Surgeon-in-Chief
Texas Children's Hospital
Houston, Texas

Alan Gaffney, MB, BCh, PhD
Assistant Professor of Anesthesiology
Department of Anesthesiology
College of Physicians & Surgeons of Columbia University
New York, New York

Jeffrey C. Gardner, MD
Assistant Professor
Department of Anesthesiology
Wake Forest School of Medicine
Winston-Salem, North Carolina

J. William Gaynor, MD
Professor of Surgery
Department of Cardiothoracic Surgery
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania

N. Martin Giesecke, MD
M.T. "Pepper" Jenkins Professor, Vice Chairman
University Hospitals
Department of Anesthesiology and Pain Management
UT Southwestern Medical Center
Dallas, Texas

Glenn P. Gravlee, MD
Professor
Vice Chair for Faculty Affairs
Department of Anesthesiology
University of Colorado School of Medicine
Anschutz Medical Campus
Aurora, Colorado

Michael S. Green, DO
Chair and Program Director
Department of Anesthesiology and Perioperative Medicine
Hahnemann University Hospital
Drexel University College of Medicine
Philadelphia, Pennsylvania

Jonathan W. Haft, MD
Associate Professor of Adult Cardiac Surgery & Anesthesia
Director
Extracorporeal Life Support Program
Associate Director
Cardiovascular Intensive Care Units

Department of Cardiac Surgery
University of Michigan Health Systems
Ann Arbor, Michigan

Richard I. Hall, MD
Professor of Anesthesiology
Critical Care Medicine and Pharmacology
Dalhousie University
Halifax, Nova Scotia, Canada

John W. Hammon, MD
Professor of Surgery, Emeritus
Department of Cardiothoracic Surgery
Wake Forest University School of Medicine
Winston-Salem, North Carolina

Deepak Hanumanthaiah, MD, FCARCSI, FRCPC
Clinical Fellow
Department of Anesthesia
St. Michael's Hospital
University of Toronto
Toronto, Ontario, Canada

Izumi Harukuni, MD
Assistant Professor
Adult Cardiac Anesthesia Division
Department of Anesthesiology and Perioperative Medicine
Oregon Health and Science University
Portland, Oregon

Eugene A. Hessel II, MD, FACS
Professor Anesthesiology, Surgery (Cardiothoracic) Neurosurgery, and Pediatrics
University of Kentucky College of Medicine
Lexington, Kentucky

Michael H. Hines, MD, FACS
Professor of Pediatric Cardiovascular Surgery
Professor of Cardiothoracic Surgery
University of Texas Medical School at Houston
Houston, Texas

Justin Horricks, MD
Cardiac Anesthesiologist
Loma Linda University Faculty Medical Group
Loma Linda, California

Jay C. Horrow, MD, MS, FACC, FAHA
Professor of Anesthesiology & Perioperative Medicine
Drexel University College of Medicine
Philadelphia, Pennsylvania

Eric Jenkins, CCT, CCP, FPP
Cardiovascular Perfusionist
University of Michigan
Detroit, Michigan

David Kiamanesh, MD
Assistant Professor of Anesthesiology and Critical Care
Columbia University College of Physicians and Surgeons
New York, New York

Mark Kurusz, CCP (Emeritus)
Division of Cardiothoracic Surgery
Adjunct Assistant Professor
Department of Surgery
The University of Texas Medical Branch
Galveston, Texas

Barry D. Kussman, MBBCh, FFA(SA)
Associate Professor of Anaesthesia
Harvard Medical School
Senior Associate in Cardiac Anesthesia
Department of Anesthesiology, Perioperative & Pain Medicine
Boston Children's Hospital
Boston, Massachusetts

Alan P. Kypson, MD, FACS
Professor and Chief of Cardiothoracic Surgery
East Carolina Heart Institute
Brody School of Medicine
East Carolina University
Vidant Medical Center
Greenville, North Carolina

Scott A. LeMaire, MD
Professor and Vice Chair for Research
Michael E. DeBakey Department of Surgery
Baylor College of Medicine
Department of Cardiovascular Surgery
Texas Heart Institute and Baylor St. Luke's Medical Center
Houston, Texas

Adair Q. Locke, MD
Assistant Professor
Section of Cardiothoracic Anesthesiology
Department of Anesthesiology
Wake Forest School of Medicine
Winston-Salem, North Carolina

Christopher E. Mascio, MD
Pediatric Cardiothoracic Surgery
The Children's Hospital of Philadelphia
Assistant Professor of Clinical Medicine
Perelman School of Medicine
University of Pennsylvania
Philadelphia, Pennsylvania

Gregory S. Matte, CCP, LP, FPP
Co-Chief of Perfusion/Clinical Coordinator
Boston Children's Hospital
Boston, Massachusetts

C. David Mazer, MD, FRCPC
Professor and Vice-Chair for Research
Department of Anesthesia
University of Toronto
Keenan Research Centre for Biomedical Science and Li Ka Shing Knowledge Institute of St. Michael's Hospital
Toronto, Ontario, Canada

Niamh A. McAuliffe, MBBCh, FCARCSI, FRCPC
Clinical Fellow
Department of Anesthesia
St. Michael's Hospital
University of Toronto
Toronto, Ontario, Canada

Noel L. Mills, MD
Department of Surgery
Division of Cardiothoracic Surgery
Ochsner Health System
New Orleans, Louisiana

Josef Nile Mueksch, MD, MBA
Providence Anesthesia Associates
Division Chief
Brunswick Novant Medical Center
Chief of Surgery
Brunswick Novant Medical Center Supply

Wilmington, North Carolina

Glenn S. Murphy, MD
Director
Clinical Research and Cardiac Anesthesia
North Shore University Health System
Clinical Professor
University of Chicago Pritzker School of Medicine
Chicago, Illinois

Mark T. Nelson, MD, Med
Assistant Professor
Fellowship Program Director
Director
Perioperative Echocardiography
Department of Anesthesiology
Virginia Commonwealth University
Richmond, Virginia

L. Wiley Nifong, MD
Associate Professor Cardiothoracic Surgery
East Carolina Heart Institute
Greenville, North Carolina

Priv. Doz. Dr. med. Andreas Pape
Associate Professor
Department of Anaesthesia
Intensive Care Medicine and Pain Therapy
University Hospital Frankfurt
Frankfurt, Germany

Steven A. Raskin, CCP
Chief Perfusionist
Baylor College of Medicine
Houston, Texas

Murphy Rayle, BA, CCP, LP
Perfusionist
Medical City Dallas
Dallas, Texas

Heather Reed, MD
Chief Resident
Department of Anesthesiology
University of Florida
Gainesville, Florida

Derek J. Roberts, BSc (Pharm), MD, PhD
Resident
Division of General Surgery
Department of Surgery
University of Calgary
Calgary, Alberta, Canada

Eduardo S. Rodrigues, MD
Assistant Professor Anesthesiology
Anesthesia Quality and Safety
Mayo Clinic Florida
Jacksonville, Florida

David M. Rothenberg, MD, FCCM
The Max S. Sadove Professor of Anesthesiology
Vice Chair, Academic Affairs & Program Director
Department of Anesthesiology
Associate Dean
Academic Affiliations
Rush University Medical Center
Chicago, Illinois

Roger L. Royster, MD, FACC
Professor and Executive Vice Chair
Department of Anesthesiology
Wake Forest School of Medicine
Winston-Salem, North Carolina

Derek A. Sanderson Jr., BS, CCP, LP
Senior Perfusionist, Chief of Pediatric Perfusion and Extracorporeal Perfusion
Department of Cardiovascular Sciences, East Carolina Heart Institute
East Carolina University
Greenville, North Carolina

Valerie Sera, MD, DDS
Clinical Associate Professor, Division Chief
Adult Cardiac Anesthesia, Anesthesiology and Perioperative Medicine
Oregon Health and Science University
Portland, Oregon

Kenneth G. Shann, CCP
Director, Perfusion Services
Massachusetts General Hospital
Boston, Massachusetts

Linda Shore-Lesserson, MD, FAHA, FASE
Professor of Anesthesiology
Hofstra Northshore-LIJ School of Medicine
Director
Cardiovascular Anesthesiology, Northshore LIJ Medical Center
New Hyde Park, New York

Robert N. Sladen, MBChB, FCCM
Allen Hyman Professor of Critical Care Anesthesiology, Executive Vice-Chair and Chief
Division of Critical Care
Medical Director
Cardiothoracic and Surgical Intensive Care Units, Department of Anesthesiology
College of Physicians & Surgeons of Columbia University
New York, New York

Larry W. Stephenson, MD
Professor Emeritus, Ford-Webber Professor of Surgery
Wayne State University
Detroit, Michigan

Robin G. Sutton, MS, CCP
Director
Biomed Training and Education Division
Biomed Simulation, Inc.
Poway, California

Ravi R. Thiagarajan, MBBS, MPH
Senior Associate in Cardiology
Cardiac Intensive Care Unit
Department of Cardiology
Boston Children's Hospital
Associate Professor of Pediatrics
Harvard Medical School
Boston, Massachusetts

Neil J. Thomas, MD
Attending Cardiac Surgeon
Northwestern Medicine-Central Dupage Hospital
Winfield, Illinois

Victoria Vasileiadou, RN
Cardiovascular Perfusionist
Department of Cardiothoracic Surgery
General Army Hospital of Athens
Athens, Greece

Jakob Vinten-Johansen, MS, PhD
Professor of Cardiothoracic Surgery (retired)
Emory University School of Medicine
Atlanta, Georgia

Nicholas Weber, DO
Staff Anesthesiologist
Infinity Healthcare
Milwaukee, Wisconsin

Kai Zacharowski, MD, PhD, FRCA
Director and Chair
Department of Anesthesiology, Intensive Care Medicine & Pain Therapy
University Hospital Frankfurt
Frankfurt, Germany

Mustafa Zakkar, PhD, MRCS
University of Bristol
Bristol Heart Institute
Bristol, United Kingdom

Preface

For the fourth edition, the editors decided that the term "Cardiopulmonary Bypass" remained relevant but insufficient, because cardiopulmonary technology has evolved to encompass both short-term and long-term forms of cardiac and pulmonary support. As a result, we have renamed this edition *Cardiopulmonary Bypass and Mechanical Support: Principles and Practice.* Our intent is for this terminology to encompass univentricular and biventricular assist devices as well as forms of pulmonary support that involve blood-gas exchange outside the lungs. In so doing, we aspire to provide a single source of broad-based information that is highly relevant to the clinical practices of cardiac surgery, cardiac anesthesiology, and perfusion technology. In addition, there is much information that is useful to all types of intensive care specialists as well as to neonatologists and interventional cardiologists. As in previous editions, we seek to provide underlying basic science principles as well as practical clinical applications. The book remains unique in its multidisciplinary comprehensive approach to this increasingly broad and complex discipline.

This edition sustains the same general organization as the third edition, but several chapters have been eliminated or merged with others, while some new ones have been added. Of note, mechanical circulatory support has been divided into short-term and long-term applications. The introductory history section brings a new perspective. Although it would seem that history is history, viewing it through different eyes reinvigorates its analysis, so the editors welcome the insightful narrative of Drs. Stephenson and Baciewicz. The editors refer readers to previous editions for the still-riveting historical accounts of C. Walton Lillehei and Harris B. Schumacker.

Editors Gravlee and Davis welcome colleagues John Hammon and Barry Kussman as coeditors. Their presence has injected new ideas and creative energy into the rewarding process of planning and assembling this book. All of the editors thank Wolters Kluwer/Lippincott Williams and Wilkins for its continued interest in and support for this important multidisciplinary subject.

Glenn P. Gravlee, MD

Richard F. Davis, MD, MBA

John W. Hammon, MD

Barry D. Kussman, MBBCh, FFA(SA)

Acknowledgments

Glenn P. Gravlee thanks his wife, Joyce, for her patience and understanding about the time one must commit to a book such as this. Despite dedicated weekday time for academic pursuits, book projects inevitably invade evenings and weekends.

Richard F. Davis thanks his wife, Elaine, for her consistent support and encouragement and for her gift of time during the many hours spent preparing the book for publication.

John W. Hammon gratefully acknowledges the support of his wife Lisa and secretary Donna Smitherman. He is thankful to have had the opportunity to learn much about perfusion technology from the teams of dedicated perfusionists during his surgical training at Duke University and later while on the faculty at Vanderbilt and Wake Forest University.

Barry D. Kussman thanks his loving wife, Belinda, and wonderful daughters, Toni and Mia, for their understanding and support during the many hours spent working on this book. He is grateful for the outstanding education and training he received in South Africa and Boston, and appreciates the support of the Department of Anesthesiology, Perioperative and Pain Medicine at Boston Children's Hospital, for this and other academic projects.

Chapter 1
Development of Cardiopulmonary Bypass

Larry W. Stephenson

Frank A. Baciewicz Jr.

INTRODUCTION

The development of cardiopulmonary bypass or a machine that could temporarily take over the function of the heart and provide oxygenation of the blood (bypass the pulmonary circuit) was a major development in clinical medicine. With the ability to bypass both the heart and lungs, surgeons were now able to correct cardiac defects, replace diseased valves, and bypass obstructed coronary arteries. It has led to the ability to remove the heart itself, and perform a transplant.

It has also been instrumental in the development of ventricular assist devices, which can be implanted on a temporary or permanent basis, to provide partial or complete perfusion for the entire body.

EARLY RESEARCH

This development was initiated in the early 1800s when physicians were experimenting with forms of external perfusion, which meant drawing blood from a living animal or person and injecting it into an excised organ or subject. The external perfusion techniques soon led to processes which infused oxygen into the perfused blood. However, it was not until Dr. Gibbon's development of the heart-lung machine in the 1950s that the dreams and aspirations of the early visionaries were realized.

In 1812, Cesar-Julian-Jean LeGallois (1) postulated that tissues and organs of dead animals could be returned to a functioning living state by restoring blood flow via a perfusion machine. This theory was based on experiments which had restored function to organs of dead animals by perfusing their organs with blood. The perfusion was by hand syringe. Similar studies followed, such as artificial perfusion of muscles and organs. In the 1850s, Charles Eduard Brown-Sequard (2) attributed the success of these perfusions of muscles and organs to oxygenated blood. He made the observation that rigor mortis temporarily disappeared from the muscles of guillotined criminals when these muscles were perfused with their own blood. His techniques for perfusing organs were rather simple—he used syringes for perfusion, and introduced oxygen into the blood by agitating the blood vigorously. Other investigators at that time, such as Waldemar Von Schroder (3), used a bubbling method or passing bubbles of air or oxygen through the blood in an attempt to increase the oxygen in these primitive perfusion systems. Unfortunately, the bubble technique resulted in significant foaming in the blood and gas embolism. The solution would await the development of antifoaming agents in the following century.

Another technique was used for introducing oxygen into the blood—the filming technique, which was developed in 1885 by Max Von Frey and Max Gruber. They were able to oxygenate blood by running blood inside a rotating cylinder filled with oxygen (4). They used this device for the perfusion of isolated organs. Other investigators at that time were also using a filming technique to oxygenate blood in their experimental apparatus. Richards and Drinker (5) directed the blood flow through a cloth cylinder inside an oxygen chamber, and Baylis dispersed the blood over a series of disks and cones and then oxygenated over with flowing oxygen (6,7). Other researchers dispersed the blood on a glass cylinder into which oxygen jets were blowing. Nevertheless, oxygenating the blood for these perfusion studies remained a difficult problem to overcome. The apparatus were very complex, utilizing very low volumes of blood per minute, and they could be maintained for only short time periods.

Investigators such as Patterson and Starling (8) and Jacob (9) oxygenated the blood by having it first perfuse through the animal's own lungs and then into the investigated organ. In that way the blood was being autooxygenated. These devices were cleverly designed, but very difficult to maintain.

These efforts at organ perfusion were taken to another level by the Russian duo Brukhonenko and Tchetchuline (10), who perfused oxygenated blood through the carotid arteries of guillotined heads of dogs, and were able to keep the head functional for several hours. The blood that was being infused into the carotid arteries was being oxygenated through the lungs of a second dog (see Fig 1.2). These experiments foreshadowed the cross-circulation work of Dr. Walt Lillehei at the University of Minnesota (10), decades later, in which he used the parent of a child as both pump and oxygenator for pediatric patients undergoing cardiac surgery.

After success with keeping the dog heads functional for several hours, Brukhonenko used a similar method of

oxygenation in an attempt to bypass the nonfunctioning hearts of dogs. Although some of these animals lived for a short period of time after termination of the experiments, he was not able to restore heart function. These studies by Brukhonenko (11) were unsuccessful, but suggested how a bypass device with an oxygenator had potential applications in humans. His foresight at this juncture regarding the possibility of being able to bypass the heart was far ahead of its time (12).

The famous aviator, Charles Lindbergh, was also involved in the research related to the heart pump. Mr. Lindbergh's sister-in-law had rheumatic fever, and at that time there were no operations for the correction of a diseased heart valve. In an effort to design a mechanical heart that would maintain blood circulation while his sister-in-law's heart was being operating on, he continually queried doctors, which eventually led to a meeting with Dr. Alexis Carrell, winner of the Nobel Prize and the director of the Rockefeller Institute for medical research (13). Dr. Lindbergh discussed his ideas with Carrell, and the potential problems such as infection, blood clotting, and hemolysis of red blood cells. Carrell was very interested in tissue culture perfusion and made the point that he had not been successful in finding an infection-free organ-perfusing device. Following these conversations, Lindbergh went to work part-time at the Rockefeller Institute in New York. He worked on trying to perfuse whole organs and was able to develop a sterile pulsatile perfusion system which could work at various flow rates and variable perfusion pressures. This work led to a picture of Carrell (13) and Lindbergh on the cover of *Time* magazine in June 1938. This pump system was able to perfuse various organs for multiple days, including a thyroid gland for 18 days in 1935 (14). They were able to grow epithelial cells of the organ in tissue cultures after that perfusion period. They were also able to keep hearts beating for several days with the pumps that they developed. These organs survived well over several days, but developed interstitial edema.

THE DEVELOPMENT OF CARDIOPULMONARY BYPASS FOR HEART SURGERY

The development of the heart-lung machine made repair of intracardiac lesions possible. Lillehei wrote, "A physician at the bedside of a child dying of an intracardiac malformation as recently as 1952 could only pray for a recovery! Today with the heart-lung machine, correction is routine" (12). To bypass the heart, one needs a basic understanding of the physiology of the circulation, a method of preventing the blood from clotting, a pump to pump blood, and finally, a method to ventilate the blood.

ANTICOAGULATION

One of the key requirements of the heart-lung machine is anticoagulation of blood. Heparin was discovered by a medical student, Jay McLean, working in the laboratory of Dr. William Howell, a physiologist at Johns Hopkins (15). In 1915, Howell gave McLean the task of studying a crude brain extract known to be a powerful thromboplastin. Howell believed that the thromboplastic activity was caused by cephalin contained in the extract. McLean's job was to fractionate the extract and purify the cephalin. McLean also studied extracts prepared from heart and liver. McLean discovered that a substance in the extract was retarding coagulation. McLean (16) wrote:

> I went one morning to the door of Dr. Howell's office, and standing there (he was seated at his desk), I said, "Dr. Howell, I have discovered antithrombin." He smiled and said, "Antithrombin is a protein and you are working with phospholipids. Are you sure that salt is not contaminating your substance?" I told him that I was sure of that, but it was [a] powerful anticoagulant. He was most skeptical, so I had the diener, John Schweinhand, bleed a cat. Into a small beaker full of its blood, I stirred all the proven batch of heparphosphotides, and placed this on Dr. Howell's laboratory table and asked him to tell when it clotted. It never did.

McLean described his finding in February 1916 at a medical society meeting in Philadelphia and later reported it in an article titled "The Thromboplastic Action of Cephalin" (16,17). Howell and Holt (18) reported their work on heparin in 1918. In the 1920s, animal experiments confirmed that heparin was an effective anticoagulant (19).

JOHN GIBBON'S EARLY RESEARCH

John Gibbon (20) probably contributed more to the success of the development of the heart-lung machine than anyone else. His interest began one night in 1931 in Boston during an all-night vigil by the side of a patient with a massive embolus:

> My job that night was to take the patient's blood pressure and pulse every 15 minutes and plot it on a chart. During the 17 hours by the patient's side, the thought constantly recurred that the patient's hazardous condition could be improved if some of the blue blood in the patient's distended veins could be continuously withdrawn into an apparatus where the blood could pick up oxygen and discharge carbon dioxide and then pump this blood into the patient's arteries. At 8 a.m. the patient's blood pressure could not be measured. Dr. Edward Churchill, the chief of surgery, immediately opened the chest through an anterior left thoracotomy, then occluded both the pulmonary artery and the aorta as they exited from the heart. He opened the pulmonary artery and removed massive blood clots. The patient did not survive.

Gibbon's work on the heart-lung machine took place over the next 20 years, in laboratories at the Massachusetts General

Hospital, the University of Pennsylvania, and Thomas Jefferson University.

In 1937, Gibbon (21) reported the first successful demonstration that life could be maintained by an artificial heart and lung and that the native heart and lungs could resume function. Unfortunately, only three animals recovered adequate cardiorespiratory function after total pulmonary artery occlusion and bypass, but they died a few hours later. Gibbon reported at the 1939 meeting of the American Association for Thoracic Surgery that the survival of cats in good condition had been achieved after a period of total CPB. Clarence Crafoord, the widely respected head of thoracic surgery at the Karolinska Institute in Stockholm, commented in response to the report that a virtual pinnacle of success in surgery had been reached. Leo Eleosser, a distinguished San Francisco surgeon, remarked that Gibbon's work reminded him of the visions of Jules Verne, thought impossible at the time but accomplished somewhat later (22).

Gibbon's work was interrupted due to his military service during World War II; afterward he resumed his work at Thomas Jefferson Medical College in Philadelphia. Meanwhile, other groups, including Clarence Crafoord in

Stockholm, Sweden, J. Jongbloed at the University of Utrecht in Holland, Clarence Dennis at the University of Minnesota, Mario Dogliotti and coworkers at the University of Turin in Italy, and Forest Dodrill at Harper Hospital in Detroit, also worked on a heart-lung machine (23).

CLARENCE DENNIS

Clarence Dennis's first clinic attempt at open-heart surgery was in a 6-year-old girl with end-stage cardiac disease. Her heart was already massive, and her only hope was surgical closure of an atrial septal defect (24). At operation on April 5, 1951, her circulation was supported by a heart-lung machine that Dennis and coworkers had developed. The atrial septal defect was very difficult to close. Although the heart-lung machine functioned well, the patient did not survive, probably because of a combination of blood loss and surgically induced tricuspid stenosis (25).

MARIO DIGLIOTTI

In August 1951, Mario Digliotti used his heart-lung machine to support the circulation in a 49-year-old patient during resection of a large mediastinal tumor. During the operation, the patient developed hypotension and cyanosis (26). He was placed on partial bypass at 1 L/min. Although the mass was resected successfully, the Italian machine was never used for open-heart surgery in humans.

FOREST DODRILL

Forest Dodrill and colleagues used the mechanical blood pump they developed with General Motors in a 41-year-old man. General Motors called it the Dodrill-GMR pump—GMR for General Motors Research laboratories, where it was developed. The machine was used to substitute for the left ventricle for 50 minutes while a surgical procedure was carried out on the mitral valve. Although Dodrill's report lacks details of the procedure and omits important hemodynamic information, it nevertheless represents a landmark in the field of cardiothoracic surgery (27). This, the first clinically successful total left-sided heart bypass, was performed on July 3, 1952, and followed from Dodrill's experimental work with a mechanical pump for univentricular, biventricular, or cardiopulmonary bypass. Dodrill had used their pump with an oxygenator for total heart bypass in animals, but he felt left-sided heart bypass was the most practical method for their first clinical case because it was not associated with a profound "hypotensive reflex" that occurred in other forms of bypass (28). When their patient was interviewed at age 68, he recalled seeing dogs romping on the roof of a nearby building from his hospital room in 1952. Later, he learned that they had been used in the final test of the Dodrill-General Motors mechanical heart machine.

Later, on October 21, 1952, Dodrill et al. (29) used their machine in a 16-year-old boy with congenital pulmonary stenosis to perform a pulmonary valvuloplasty under direct vision; this was the first successful right-sided heart bypass.

Between July 1952 and December 1954, Dodrill performed approximately 13 clinical operations on the heart and thoracic aorta using the Dodrill-General Motors machine, with at least five hospital survivors. While he used this machine with an oxygenator in the animal laboratory, he did not start using an oxygenator with the Dodrill-General Motors mechanical heart clinically until early 1955 (30).

WILFRED BIGELOW

Hypothermia was another method to stop and open the heart. In 1950, Bigelow et al. (31) reported on 20 dogs that had been cooled to 20°C, with 15 minutes of circulatory arrest; 11 animals also had a cardiotomy. Only six animals survived after rewarming. Bigelow and colleagues continued to study hypothermia and hibernation and learned that a groundhog could be cooled to a body temperature of 5°C and be revived (32,33). This temperature allowed circulatory arrest with a cardiotomy procedure lasting 2 hours without ill effects (34).

JOHN LEWIS

In 1953, F. J. Lewis and M. Taufic (35) reported on 26 dogs that had surgically induced atrial septal defects which they attempted to close using a hypothermia technique. In this paper, the authors also reported on a 5-year-old girl who had closure of her atrial septal defect on September 2, 1952, using a hypothermic technique.

She was anesthetized and the trachea was intubated. She was then wrapped in refrigerated blankets until after a period

P.6

of 2 hours and 10 minutes her rectal temperature had fallen to 28°C. At this point, the chest was entered through the bed of the right 5th rib. The cardiac inflow was occluded for a total of 5½ minutes and during this time the septal defect measuring 2 cm in diameter was closed under direct vision. The patient was rewarmed by placing her in hot water kept at 45°C; after 35 minutes, her rectal temperature had risen to 36°C, at which time she was removed from the bath. Recovery from the anesthesia was prompt and her subsequent postoperative convalescence was uneventful.

This was the first successful repair of an atrial septal defect in a human with surface cooling under direct vision. Shortly after, Swan et al. (36) reported successful results in 13 clinical cases using a similar technique. The use of systemic hypothermia for open intracardiac surgery was relatively short-lived. After the heart-lung machine was introduced clinically, it appeared that deep hypothermia was obsolete. However, during the 1960s, it became apparent that operative results in infants under 1 year of age using cardiopulmonary bypass were poor. In 1967, Hikasa et al. (37), from Kyoto, Japan, published an article that reintroduced profound hypothermia for cardiac surgery in infants and used the heart-lung machine for rewarming. Their technique involved surface cooling to 20°C, cardiac surgery during circulatory arrest for 15 to 75 minutes, and rewarming with cardiopulmonary bypass. At the same time, other groups reported using profound hypothermia with circulatory arrest in infants with the heart-lung machine for cooling and rewarming (38,39,40,41). Results were much improved, and subsequently the technique was applied also for resection of aortic arch aneurysms in adults.

GIBBON'S RESEARCH CONTINUES

After World War II, John Gibbon resumed his research. He eventually met Thomas Watson, chairman of the board of the International Business Machines (IBM) Corporation. Watson was fascinated by Gibbon's research and promised help. Soon afterward, six IBM engineers arrived and built a machine that was similar to Gibbon's earlier machine, which contained a rotating vertical cylinder oxygenator and a modified DeBakey rotary pump. Gibbon successfully used this new machine for intercardiac surgery on small dogs and had several longterm survivors, but the blood oxygenator was too small for patients. Eventually, the team developed a larger oxygenator that the IBM engineers incorporated into a new machine (42).

In 1949, Gibbon's early mortality in dogs was 80%, but it gradually improved (23). The first patient was a 15-monthold girl with severe congestive heart failure. The preoperative diagnosis was atrial septal defect, but at operation, none was found. She died, and a huge patient ductus was found at autopsy. The second patient was an 18-year-old girl with congestive heart failure also due to an atrial septal defect. This defect was closed successfully on May 6, 1953, with the Gibbon-IMB heart-lung machine. The patient recovered, and several months later, the defect was confirmed closed at cardiac catheterization. This was the first successful clinical case using the heart-lung machine (43). Unfortunately, Gibbon's next two patients did not survive intracardiac procedures when the heart-lung machine was used. These failures distressed Dr. Gibbon, who declared a 1-year moratorium for the heart-lung machine until more work could be done to solve the problem causing the deaths.

C. WALTON LILLEHEI

During this period, C. Walton Lillehei and colleagues at the University of Minnesota studied a technique called *controlled cross-circulation*. With this technique, the circulation of one dog was temporarily used to support that of a second dog while the second dog's heart was temporarily stopped and opened. After a simulated repair in the second dog, the animals were disconnected and allowed to recover, Lillehei (44) remarked.

Clinical cross-circulation for intracardiac surgery was an immense departure from the established surgical practice. This thought of taking a normal human to the operating room to serve as a donor circulation (with potential risk, however small), even temporarily, was considered by critics of the time to be unacceptable, even "immoral" as one prominent surgeon was heard to say. Some others, skilled in the art of criticism, were quick to point out that this proposed operation was the first in all of surgical history to have the potential (even the probability in their judgment) for a 200% mortality.

However, the continued lack of any success in the other centers around the world that were working actively on heart-lung bypass led to the decision to go ahead inevitable. I felt the technique was ready to use in man; however, even in such a progressive and pioneering medical school as Minnesota University, there was opposition to the idea. Dr. Owen Wangenstein, chairman of the Department of Surgery, was a tremendous help. He was well aware of these experiments and whole-heartedly supported them. Where there seemed a possibility that the first clinical operation might be canceled the night before because of this opposition, I left a note for Dr. Wangenstein asking, "Is our case still on in the morning?" His answer, "Dear Walt, by all means, go ahead."

Lillehei et al. (12) used their technique at the University of Minnesota to correct a ventricular septal defect (VSD) in a 12-month-old infant on March 26, 1954. The patient had been hospitalized for 10 months for uncontrollable heart failure and pneumonitis. At operation, a 2-cm membranous VSD was closed with suture. The patient made an uneventful recovery until death on the eleventh postoperative day from a rapidly progressing tracheal bronchitis. At autopsy, the VSD was closed, and the respiratory infection was confirmed as the cause of death. Two weeks later, the second and third patients had VSDs closed by the same technique 3 days apart. Both remained long-term survivors with normal hemodynamics confirmed by cardiac catheterization.

In 1955, Lillehei et al. (45) published a report of 32 patients which included repairs of VSDs, tetralogy of Fallot, and atrioventricularis communis defects. By May 1955, the pump used for systemic cross-circulation by Lillehei et al. was coupled with a bubble oxygenator developed by Drs. DeWall and Lillehei. Cross-circulation was abandoned after use in 45 patients during 1954 and 1955. Although its clinical use was short-lived, clinical cross-circulation was an important stepping stone in the development of cardiac surgery (44).

JOHN W. KIRKLIN

Meanwhile, at the Mayo Clinic only 90 miles away, John W. Kirklin and colleagues (46) launched their open-heart program on March 5, 1955. They used a heart-lung machine based on the Gibbon-IBM machine but with their own modifications. Dr. Kirklin (47) wrote:

> In 1951, now on the surgical staff on the Mayo Clinic, I did a closed pulmonary valvulotomy on a 30-year-old man with pulmonary stenosis and intact ventricular septum. He had massive ventricular hypertrophy and died about 2 days after the operation. At autopsy it was apparent that the pulmonary valve was open, but also that the subvalvular muscle hypertrophy was enormous. The patient could not survive without relief of the muscular obstruction. Dr. Earl Wood, a great physiologist and my co-worker and I went back to his office after we viewed that autopsy and decided that we would either have to be content with cardiac surgery as a rather minor specialty, limited to passing instruments into the heart or we would need a heart-lung machine. In earlier times, Earl Wood had worked with

Maurice Visshher at the University of Minnesota and had experience with the Starling heart-lung preparation. “It’s the oxygenator that is the problem,” said Earl Wood.

Kirklin (47) goes on to say:

We investigated and visited the groups working intensively with the mechanical pump oxygenators. We visited Dr. Gibbon in his laboratories in Philadelphia, and Dr. Forest Dodrill in Detroit, among others. The Gibbon pump oxygenator had been developed and made by the International Business Machine Corporation and looked quite a bit like a computer. Dr. Dodrill’s heart-lung machine had been developed and built for him by General Motors and it looked a great deal like a car engine. We came home, reflected and decided to try to persuade the Mayo Clinic to let us build a pump oxygenator similar to the Gibbon machine, but somehow different. We already had had about a year’s experience in the animal laboratory with David Donald using a simple pump and bubble oxygenator when we set about very early in 1953, the laborious task of building a Mayo Gibbon pump oxygenator and continuing the laboratory research.

Most people were very discouraged with the laboratory progress. The American Heart Association and the National Institute of Health had stopped funding any projects for the study of heart-lung machines, because it was felt that the problem was physiologically insurmountable. David Donald and I undertook a series of laboratory experiments lasting about a year and a half during which time the engineering shops at the Mayo Clinic constructed a pump oxygenator based on the Gibbon model (48).

Of course a number of visitors came our way and some of them came to the laboratory to see what we were doing. One of those visitors was Ake Senning (from Stockholm, Sweden). I still remember the day when he was there and one of the connectors came loose and we ruined his beautiful suit as well as the ceiling of the laboratory by spraying blood all around the room.

The electrifying day came in the spring of 1954 when the newspapers carried an account of Walt Lillehei’s successful open heart operation on a small child. Of course, I was terribly envious and yet I was terribly admiring at the same moment. That admiration increased exponentially when a short time later, a few of my colleagues and I visited Minneapolis and observed one of what was now a series of successful open-heart operation with control cross-circulation. Walt then took us on rounds and it was absolutely exciting to see children recovering from these miraculous operations. However, it was also for a time, a difficult period for me. Some of my colleagues at the Mayo Clinic, and some of my influential ones, indicated to me that we had wasted much time and money. After all, this young fellow in Minneapolis was successful with a very simple apparatus and did not even require an oxygenator. Visitors coming from Minneapolis to Rochester asked, “What are you working on these days?” When I said we were working with an integrated pump oxygenator, most said, “Oh, yes, but I understand even Gibbon had given up.” As the months went by, my anxiety grew and I was worried that we too might not make the effort a successful one. My apprehension was heightened early in 1955 when Time magazine published an interview with Dick Varco, who described all too accurately the damaging effects of artificial oxygenators and why they were impractical and dangerous.

However, in the winter of 1954 and 1955, we had 9 surviving dogs out of 10 cardiopulmonary bypass runs. With my wonderful colleague and pediatric cardiologist,

Jim DuShane, we had earlier selected eight patients for intracardiac repair. Two had to be put off because two babies with very serious congenital heart disease came along and we decided to fit them into the schedule. We had determined to do [the repair in] all eight patients even if the first seven died. All of this was planned with the knowledge and approval of the governance of the Mayo Clinic. Our plan was then to return to the laboratory and spend the next 6 to 12 months solving the problems that had arisen in the first planned clinical trial of a pump oxygenator. Gibbon, of course, had done a successful case in 1953, but it was an isolated case and the next four patients died. In the deepest recesses of my heart, I felt that those four patients died in part because of the lack of appreciation of some of the technical aspects of the cardiac surgery.

Kirklin (47) goes on to state:

> We did our first open heart operation on Tuesday in March 1955. That evening I had a telephone call from Dick Varco in Minneapolis, who indicated that Sir Russell Brock was visiting their cardiac surgical program at the University of Minnesota at that time. Walt Lillehei and Dick Varco indicated to Sir Russell that we had done the operation earlier that day and they called to see if he could come to Rochester the next day to see the patient, to which I said “Certainly.” I was afraid that they would ask if we had planned to do another case, and they did. I replied: Yes, and we will be doing another case on Thursday.” They asked if Sir Russell could watch the operation. Well, as you can imagine, I had enough on my mind without having a world-famous surgeon sitting in the gallery watching this young guy try to work his way through the second open heart operation. However, we acceded to Sir Russell’s coming and I am happy to say he was a marvelous guest during the second operation, and the patient did well as had the first one.

Kirklin (47) continued:

> Four of our first eight patients survived, but the press of the clinical work prevented our ever being able to return to the laboratory with the force that we had planned. By now, Walt Lillehei and I were on parallel, but intertwined paths. I witnessed an earlier parallel pathway existing between Dwight Harken and Charles Bailey in the first days of closed mitral valve surgery. I felt, and I hope you will forgive me, that their interactions were in some ways demeaning to themselves and to the scientific progress of cardiac surgery. I am extremely grateful to Walt Lillehei and am very proud of the two of us, that during that 12 to 18 months when we were the only surgeons in the world performing open intracardiac operations with cardiopulmonary bypass and surely in intense competition with each other, we shared our gains and losses with each other. We continued to communicate and we argued privately in nightclubs and on airplanes rather than publicly over our differences. Walt was more cheerful and more optimistic than I when we discussed problems. I remember saying to him one day, “Walt, I am so discouraged with complete atrial ventricular canal.” “Oh, sure,” he said, “that is a tough lesion, but we will learn to do well with it.”

DEVELOPMENT AND EVOLUTION OF THREE KEY COMPONENTS OF HEART-LUNG MACHINES: PUMPS, OXYGENATORS, AND HEAT EXCHANGERS

This section follows the development of pumps, oxygenators, and heat exchangers from those used by the heart surgery pioneers through their evolution to the present day.

Pumps

When Dr. Gibbon was developing cardiopulmonary devices in the animal laboratory, he used rubber finger cot pumps. The pumps were derived from the Dale-Schuster modification of the deBurgh-Daly pumps (49,50). These pumps used flap valves made from rubber stoppers to keep the flow unidirectional, and the flow resulted from alternately compressing and expanding the finger cot with compressed air. The Gibbons device limited the total flow that could be achieved, and the best output that Dr. Gibbon could achieve in his animal model was 500 cc/min. The Dodrill-General Motors pump also used a variation of the finger cot pump, which they developed and could pump up to 4 L/min. It was used clinically from 1952 through at least 1956 (30) (Fig. 1.1).

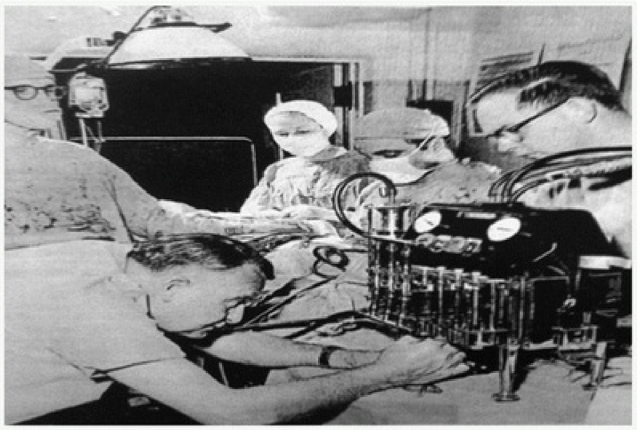

FIGURE 1.1. Dodrill-GMR mechanical pump being used in the animal laboratory with the row of finger cot pumps being adjusted.

After Gibbon returned from his stint with Pennsylvania Hospital's Evacuation Hospital Unit during World War II, he fortuitously received help from IBM to develop a cardiopulmonary bypass machine. The pump now utilized was the DeBakey-Schmidt modification of the Porter-Bradley roller pump (51).

The DeBakey-Schmidt modification of the roller pump added a flange to the outer circumference of the blood tubing which prevented its migration in the rigid housing. The roller pump also eliminated the need for valves in the Dale-Schuster pump. DeBakey had suggested to Gibbon years earlier that the roller pump should be the preferred method of perfusion in the heart-lung machine. DeBakey's contribution was not so much the modification of the roller pump, but rather the concept of using the roller pump for the bypass machine. Subsequently, improvements were made by Melrose in 1959 (52) to place a grooved plate in the housing and match the radii of the roller pump and the groove to decrease blood trauma.

The roller pump (Fig. 1.2) uses tubing which is encased within a curved runway such that one roller or clamp is always compressing the tubing (52). In this way, blood is always being pushed ahead of the roller giving a continuous blood flow. The output can be calculated from the revolutions of the roller pump per minute, and the volume per revolution. Roller pumps have been used since the 1950s, and are still in use today.

The roller pump's advantages are that it is afterload-independent and has a low priming volume and no potential for reversal of flow. The roller pump's afterload independence means that it delivers the calculated output regardless of the patient's peripheral vascular resistance, which varies depending on temperature, pH, and intrinsic tone. A disadvantage is that excessive line pressure will develop if the outflow becomes occluded with the pressure in the tubing progressively increasing until the tubing either disconnects or breaks (53). Other disadvantages are the possibility of creating high negative pressure with the production of air bubbles or cavitation, and the capacity to pump grossly visible air. In addition, the roller pump can cause damage to the tubing with possible micro emboli and rupture of the tubing, and the possibility of a large air embolus. The roller pump requires close attention to address these potential problems while on cardiopulmonary bypass.

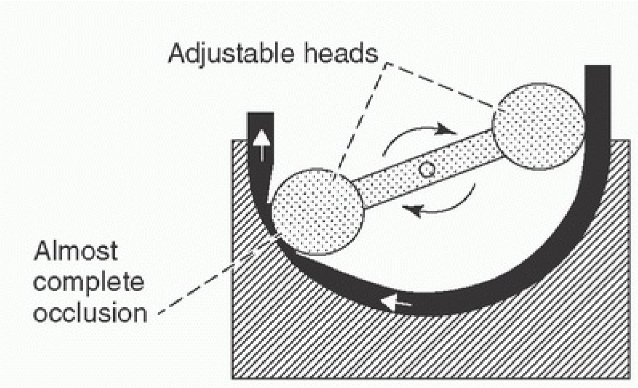

FIGURE 1.2. Diagram of Debakey-Schmidt pump utilized in the Gibbon-IBM cardiopulmonary bypass machine.

Another positive displacement pump is the Sigma motor pump, which propelled blood via a series of keys pressing in sequence against the resilient pump tubing (50). This pump was used in the 1950s at the University of Minnesota by Lillehei in the cross-circulation cases. This pump (Fig. 1.3) was eventually replaced by the roller pump, which caused less red blood cell damage.

In 1976, the Medtronic centrifugal pump became available. The first centrifugal pump was developed in the 17th century by Denis Papin (54). The centrifugal pump used for heart surgery consists of an impeller with flanges mounted on a rotating central shaft, inside a plastic housing. The central shaft is coupled magnetically with an electric motor. The magnet inside the pump head moves in conjunction (53,54) with another magnet in the drive console. The blood enters through the eye of the plastic housing, is caught up in the impeller blades, and is swirled radially through the output part of the housing. As the centrifugal pump rotates more rapidly, it creates a pressure differential resulting in blood flow (Fig. 1.4). A Doppler flow meter is required on the outflow side of the centrifugal pump to measure forward blood flow and the speed of rotation. The afterload of the arterial line determines the forward flow. In the event input to the centrifugal pump decreases, the pump outflow decreases and if air enters the circuit, the afterload increases so that only a small amount of air is pumped out before the pump revolutions cease.

The centrifugal pump is considered to have advantages over the roller pump, and is used in most cardiac operating rooms today. The advantages are that the centrifugal pump cannot develop excessive arterial pressures, is preload-dependent, afterload-dependent, and has a decreased risk of pumping significant amounts of air into the arterial line. The disadvantages are its higher cost compared to roller pumps, larger priming volume, the potential for reversal of flow if an

arterial check valve is not used, and the less precise measurement of flow generated by the pump (55).

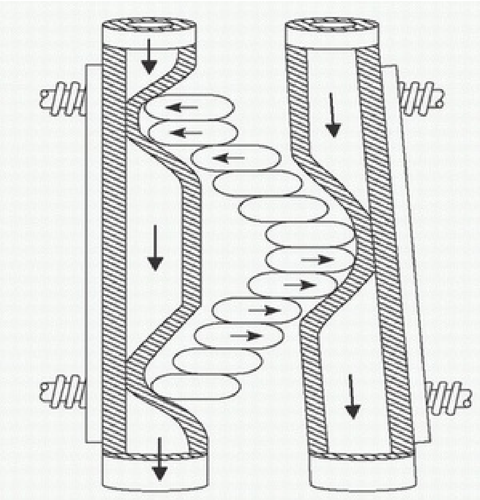

FIGURE 1.3. Diagram of Sigma motor pump with series of keys pressing in sequence against resilient tubing.

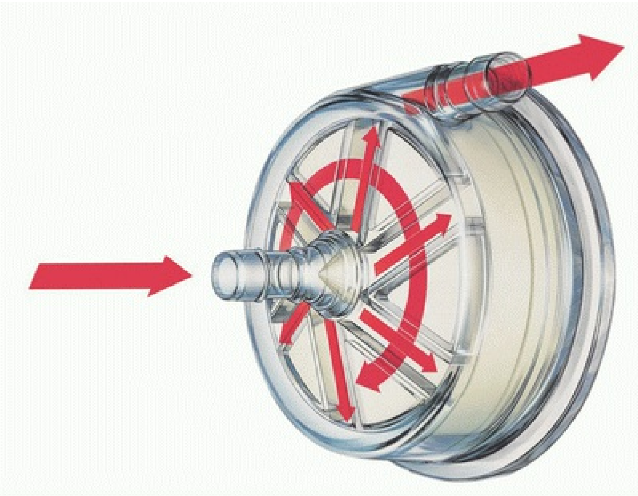

FIGURE 1.4. Diagram depicting blood flow as it enters centrifugal pump, its route through the pump as the impeller blades spin around, and then exits pump.

Currently, most heart surgery teams use the centrifugal pump for their arterial bypass, and roller pumps for cardioplegia delivery, suction, and ventricular decompression.

Oxygenators

The various groups working on the heart-lung machine in the laboratory during the early 1950s, and some even earlier, developed several different types of devices to oxygenate the venous blood returning from the animal to the excorporeal apparatus. These oxygenators worked on the principle of spreading the blood out into a thin layer over a relatively large surface area where the blood was exposed to oxygen, which caused it to give up CO_2 and take on the oxygen. Some of the devices had moving parts, such as the disk rotating oxygenator, while others were completely stationary. It was discovered that causing some degree of turbulence of the blood as it flowed over the surface improved the oxygen uptake of the blood. Too much turbulence, however, caused damage to the blood elements.

John Gibbon's research group in Philadelphia, Pennsylvania, found that if they passed the blood over a stationary screen it caused enough turbulence to significantly increase the oxygen uptake by the blood. They used such an oxygenator, incorporating several of these stationary screens in their first clinical cases, including the patient with the successful outcome in 1953 (43). At the Mayo Clinic, John Kirklin, who built a similar heart-lung machine, also used a stationary-screen oxygenator for their clinical work starting in March 1955 (46).

Meanwhile, C. Walton Lillehei's group at the University of Minnesota had been performing pediatric open-heart surgery using the cross-circulation method, wherein an adult was connected to the child's circulation and that adult's lungs served as the oxygenator while the child's heart was repaired (45). During the winter of 1954-1955, Dr. Richard DeWall, working in Dr. Lillehei's research laboratory, developed an oxygenator whereby oxygen was bubbled through the returning venous blood. As the red blood cells came in contact with the bubbles, they gave off CO_2 and took on O_2. This method was found to be very effective. DeWall then rapidly worked out methods to prevent the blood, which still contained bubbles, from returning to the patient with these bubbles, which would cause gas emboli.

The University of Minnesota group began clinically using a heart-lung machine with DeWall's bubble oxygenator in May 1955 (56). Sometime after, they developed a disposable plastic version that was made available for commercial use. Dr. Denton Cooley from Houston, Texas, visited the University of Minnesota in 1955 and observed the DeWall oxygenator. Upon his return to Houston, he set about to develop his own version, which he did. Like the DeWall oxygenator, Cooley's was made of plastic, disposable, and became commercially available. By the early 1970s, the bubble oxygenators became the oxygenator of choice at most centers performing open-heart surgery. Because they were made of disposable plastic, they did not require the long and intense effort needed to clean the screen and disk oxygenators after each use, and they required less blood prime.

Willem Kolff, a physician living in the Netherlands in the 1940s, conducted research in renal dialysis technology that ultimately led to renal dialysis becoming a clinical reality. He later immigrated to the United States, and as a researcher at the Cleveland Clinic, he developed a disposable membrane oxygenator for experimental use in 1956 (57). George Clowes and William Neville, working at Western Reserve University Medical School and at Cleveland City Hospital, developed their own variant of the membrane oxygenator. They became pioneers in using it clinically for open-heart surgery in 1958 (58,59,60).

The choice of material used to build the membrane oxygenator is important because it must be compatible with blood, permeable to O_2 and CO_2, and very thin, with minimal resistance to blood and respiratory gas flow (61). In recent years, the membrane oxygenator has replaced the bubble oxygenator in the United States because it has been proven to be safer: it produces less particulate and micro emboli, is less reactive to blood elements, and allows superior control of blood gases (62).

Blood Heat Exchanger

In 1956, Dr. Ivan Brown from Duke University asked the Harrison Radiator Division of General Motors if company engineers could design a device that would allow the cooling and heating of blood as needed during a heart operation. The device would be used in conjunction with the heart-lung machine. Prior to this time, if hypothermia was required during a procedure, the patient's body temperature was lowered by a refrigerated blanket or by ice packs. This necessitated 1 to 2 hours under anesthesia before the operative procedure could begin. Rewarming the patient after the heart repair was complete could take another 3 to 4 hours.

Working on this project were, from Duke University, Drs. Brown, Will Sealy, W. Glenn Young, and Wirt Smith. The Harrison engineering research team included W.O. Emmons, D.B. Sacca, and C.C. Eckles. The project took 10 months of planning and experimentation. The resulting blood heat exchanger consisted of a group of slender stainless steel tubes enclosed in a steel jacket. As the blood flowed through the tubes, water circulated within the steel jacket outside the tubes. Hot and cold water were directed through a special mixing valve in conjunction with a thermostat, so that the exact desired temperature could be controlled and maintained (63,64,65). The heat exchanger was placed upstream from the oxygenator in the heart-lung machine circuit, which allowed the patient's body temperature via the blood to be either cooled or warmed. The application of heat exchangers for open-heart surgery soon became standard.

In 1966, Dr. Richard DeWall made a significant advance in oxygenator design when he developed the hard-shell bubble oxygenator with an integrated heat exchanger. The entire unit was disposable and set the standard for bubble oxygenators (66). Most membrane oxygenator units incorporate the heat exchanger upstream to the oxygenator to avoid possible bubble emboli formation during rewarming.

A BUMPY ROAD DURING THE EARLY'50s

Table 1.1 is meant to further emphasize two aspects of this chapter. The first is to show the bumpy clinical road heart surgery pioneers traveled from 1951 through 1955. The second is to underscore the fact that although Dr. John Gibbon's successful case using a heart-lung machine in May 1953 was of monumental importance, more work was necessary on the heart-lung machine and understanding its physiologic effects before open-heart surgery could progress to the next level, which was widespread clinical application. This work would occur over the next couple of years.

By the end of 1956, many university groups around the world had launched into open-heart programs. Currently, it

P.12

P.13

is estimated that more than 500,000 cardiac operations are performed each year worldwide with the use of the heart-lung machine. In most cases, the operative mortality is quite low, approaching 1% for some operations. Little thought is given to the courageous pioneers in the 1950s whose contributions made all this possible.

TABLE 1.1. Clinical status of open-heart surgery, as well as blood pumps and oxygenators (1951 through 1955)

1951	**April 6**: Clarence Dennis at the University of Minnesota used a heart-lung machine to repair an ostium primum or AV canal defect in a 5-yearold girl. The patient could not be weaned from cardiopulmonary bypass (24). **May 31**: Dennis attempted to close an atrial septal defect using heart-lung machine in a 2-year-old girl who died intraoperatively of a massive air embolus (25). **August 7**: Achille Mario Digliotti at the University of Turin, Italy, used a heart-lung machine of his own design to partially support the circulation (flow at 1 L/min for 20 minutes) while he resected a large mediastinal tumor compressing the right side of the heart (26). The cannulation was through the right axillary vein and artery. The patient survived. This was the first successful clinical use of a heart-lung machine, but the machine was not used as an adjunct to heart surgery.
1952	**February** (1952 or 1953, John Gibbon; see February 1953) **March**: John Gibbon used his heart-lung machine for right-sided heart bypass only while surgeon Frank Allbritten at Pennsylvania Hospital, Philadelphia operated to remove a large clot or myxomatous tumor suspected by angiogram. No tumor or clot was found (75). The patient died of heart failure in the operating room shortly after discontinuing right-sided heart bypass. **April 3**: James Helmsworth and associates at Cincinnati General Hospital used a pump oxygenator of their own design to treat a patient suffering from end-stage lung disease. During the 75-minute pump run, partial veno-veno bypass was used. The patient's symptoms improved but recurred soon after bypass was discontinued. Samples for arterial blood saturation were taken from an indwelling needle placed in the brachial artery. The control prebypass sample was not suitable for analysis. During bypass, the arterial O2 saturation varied from 58% to 65% and dropped to 43% after bypass was discontinued (76).

July 3: Dodrill used the Dodrill-GMR pump to bypass the left side of the heart while he repaired a mitral valve. The patient survived. This was the first successful use of a mechanical pump for total substitution of the left ventricle in a human being (27).
September 2: John Lewis, at the University of Minnesota, closed an atrial septal defect under direct vision in a 5-year-old girl. The patient survived. This was the first successful clinical heart surgery procedure using total-body hypothermia. A mechanical pump and oxygenator were not used. Others, including Dodrill, soon followed, using total-body hypothermia techniques to close atrial septal defects (ASDs) and perform pulmonary valvulotomies. By 1954, Lewis reported on 11 ASD closures using hypothermia with two hospital deaths (35). He also operated on two patients with ventricular septal defect (VSD) in early 1954 using this technique. Both resulted in intraoperative deaths.
October 21: Dodrill performed pulmonary valvulotomy under direct vision using Dodrill-GMR pump to bypass the right atrium, ventricle, and main pulmonary artery. The patient survived (29).
Although Dr. William Mustard in Toronto would describe a type of "corrective" surgical procedure for transposition of the great arteries (TGA), in 1964, which, in fact, for many years, would become the most popular form of surgical correction of TGA, his early results with this lesion were not good. In 1952, he used a mechanical pump coupled to the lung that had just been removed from a monkey to oxygenate the blood in seven children while attempts were made to correct their TGA defect (77). There were no survivors.

1953 **February (or 1952)**: Gibbon at Jefferson Hospital in Philadelphia operated to close an ASD. No ASD was found. The patient died intraoperatively. Autopsy showed a large patent ductus arteriosus (78).
May 6: Gibbon used his heart-lung machine to close an ASD in an 18-year-old woman with symptoms of heart failure. The patient survived the operation and became the first patient to undergo successful open-heart surgery using a heart-lung machine (78).
July: Gibbon used the heart-lung machine in two 5-year-old girls to close atrial septal defects. Both died intraoperatively. Gibbon was extremely distressed and declared a moratorium on further cardiac surgery at Jefferson Medical School until more work could be done to solve problems related to heart-lung bypass. These were probably the last heart operations he performed using the heart-lung machine.

1954 **March 26**: C. Walton Lillehei and associates at the University of Minnesota closed a VSD in a 15-month-old boy using a technique to support the circulation that they called controlled cross-circulation. An adult (usually a parent) with the same blood type was used more or less as the heart-lung machine. The adult's femoral artery and vein were connected with tubing and a pump to the patient's circulation. The adult's heart and lung oxygenated and supported the circulation while the child's heart defect was corrected. The first patient died 11 d postoperatively from pneumonia, but six of their next seven patients survived (79). Between March 1954 and the end of 1955, 45 heart operations were performed by Lillehei on children using this technique before it was phased out. Although controlled cross-circulation was a short-lived technique, it was an important stepping stone in the development of open-heart surgery.
July: Clarence Crafoord and associates at the Karolinska Institute in Stockholm, Sweden used a heart-lung machine of their own design coupled with total-body hypothermia (patient was initially submerged in an ice-water bath) to remove a large atrial myxoma in a 40-year-old woman (80). She survived.

1955	**March 22**: John Kirklin at the Mayo Clinic used a heart-lung machine similar to Gibbon's but with modifications his team had worked out over 2 yr in the research laboratory, to successfully close a VSD in a 5-year-old patient. By May of 1955, they had operated on eight children with various types of VSDs, and four were hospital survivors. This was the first successful series of patients (i.e., more than one) to undergo heart surgery using a heart-lung machine (48). **May 13**: Lillehei and colleagues began using a heart-lung machine of their own designed to correct intracardiac defects. By May of 1956, their series included 81 patients. Initially they used their heart-lung machine for lower-risk patients and used controlled cross-circulation, with which they were more familiar, for the higher-risk patients. Starting in March 1955, they also tried other techniques in patients to oxygenate blood during heart surgery, such as canine lung, but with generally poor results (79). Dodrill had been performing heart operations with the GM heart pump since 1952 and used the patient's own lungs to oxygenate the blood. Early in the year 1955, he attempted repairs of VSDs in two patients using the heart pump, but with a mechanical oxygenator of his team's design both died. On December 1, he closed a VSD in a 3-year-old girl using his heart-lung machine. She survived. In May 1956, at the annual meeting of the American Association for Thoracic Surgery, he reported on six children with VSDs, including one with tetralogy of Fallot, who had undergone open-heart surgery using his heart-lung machine. All survived at least 48 hr postoperatively. Three were hospital survivors, including the patient with tetralogy of Fallot (81). **June 30**: Clarence Dennis, who had moved from the University of Minnesota to the State University of New York, successfully closed an ASD in a girl using a heart-lung machine of his own design (82). Mustard successfully repaired a VSD and dilated the pulmonary valve in a 9-month-old child with a diagnosis of tetralogy of Fallot using a mechanical pump and a monkey lung to oxygenate the blood. He did not give the date in 1955, but the patient is listed as Human Case 7 (83). Unfortunately, in the same report, cases 1-6 and 8-15 operated on between 1951 and the end of 1955 with various congenital heart defects did not survive the surgery using the pump and monkey lung, nor did another seven children in 1952, all with TGA (see timeline for 1952) using the same bypass technique.

Note: This list is not all-inclusive but likely includes most of the historically significant clinical open-heart events in which a blood pump was used to support the circulation during this period.

EXTRACORPOREAL LIFE SUPPORT

Extracorporeal life support (ECLS) is an extension of cardiopulmonary bypass. Cardiopulmonary bypass initially was limited to no more than 6 hours. The development of membrane oxygenators in the 1960s permitted longer support. Donald Hill and colleagues, in 1972, treated a 24-year-old man who developed shock lung after blunt trauma (67). The patient was supported for 75 hours using a heart-lung machine with a membrane oxygenator, cannulated via the femoral vein and artery. The patient was weaned and recovered. Hill's second patient was supported for 5 days and recovered. This led to a randomized trial supported by the National Institutes of Health to determine the efficacy of this therapy for adults with respiratory failure. The study was conducted from 1972 to 1975 and showed no significant difference in survival between patients managed by extracorporeal life support (9.5%) and those who received conventional ventilator therapy (8.3%) (68). Because of these results, most US centers abandoned efforts to support adult patients using ECLS, also known as *extracorporeal membrane oxygenation* (ECMO).

One participant in the adult trial decided to study neonates. The usual causes of neonatal respiratory failure have in common abnormal postnatal blood shunts known as *persistent fetal circulation* (PFC) (69,70,71,72). This is a temporary, reversible phenomenon. In 1976, Bartlett and colleagues, at the University of Michigan, were the first to successfully treat a neonate using ECLS. Since that time, two prospective studies have shown the efficacy of ECLS for management of neonatal respiratory failure. More than 8,000 neonatal patients have been treated worldwide with a survival rate of 82% (ELSO registry data) (73,74).

KEY *Points*

- Early attempts to oxygenate the blood of animals in vitro dating from 1812 are discussed. Then, various methods to perfuse animals with oxygenated blood during this early period are described.
- Famous aviator Charles Lindbergh, working with Nobel Laureate Alexis Carrel during the 1930s, developed methods to keep isolated perfused organs alive for several days.
- Jay McLean, working in William Howell's laboratory, isolated heparin in 1915 and studied its effects as an anticoagulant. This was an important discovery for those researchers who would begin to work on the heart-lung machine since it was a practical way to rapidly anticoagulate blood, and heparin's effects could also be quickly reversed.
- During the 1930s, John Gibbon began his work on developing a heart-lung machine and although his efforts toward that goal seemed slow, he continued to make progress until his research was interrupted by his military service in World War II.
- After the War, Gibbon resumed his research, but by then a number of other physician researchers had begun their own work in this field. Among them were Clarence Crafoord in Sweden, Mario Digliotti in Italy, and Clarence Dennis and Forest Dodrill in the United States.
- Wilfred Bigelow in Canada and John Lewis in Minnesota worked independently with total-body hypothermia in laboratory animals as an alternative means to protect the brain, heart, and other body organs while the heart was stopped in order to be repaired.
- On July 3, 1952, Dodrill used a blood pump to bypass the left heart in a patient while he repaired the mitral valve. The patient survived. Dodrill did not use a mechanical oxygenator but rather the patient's own lungs to oxygenate the blood during the procedure.
- Two months later, Lewis used total-body hypothermia to close a child's atrial septal defect. That patient survived.
- Gibbon had developed a heart-lung machine with both a pump and an oxygenator, and on May 6, 1953, he used this machine to support a patient's circulation while repairing a heart defect. The patient survived, and this became the first successful clinical case in which a heart-lung machine was used.
- Over the next few years, a number of other successful cases by other surgeons were performed, using various methods to pump blood to the patient and oxygenate it while repairing the heart. During this period, however, mortality rates were very high, but as more knowledge was gained in this new field of surgery the mortality rates gradually decreased.
- The development and evolution of three key components of the heart-lung machine are presented from their inception to the present: pumps, oxygenators, and heat exchangers.

REFERENCES

1. LeGallois CJJ. *Experiences sur le principe de la vie, notamment sur celui des mouvemens du Coeur, et*

sur le siege de ce principe; survies du rapport fait a la premiere classe de l'Institut sur celles relatives aux mouvemens du Coeur. Paris, UK: d'Hautel, 1812.

2. Brown-Sequard CE. Recherches experimentales sur les proprieties physologiques et les usages du sang rouge et du sang noir et de leurs principaux elements gazeux, l'oxygene et l'acide corbonique. *J Physiol Homme* 1858;1:729-735.

3. Von Schroder W. Uber die bildungstatte des harnstoffs. *Arch Exp Pathol Pharmacol* 1882;15:364-402.

4. Von Frey M. Gruber M. Untersuchungen uber den stoffwechsel isolierte organe. Ein respiration-apparat fur isolierte oregano. *Virchow's Arch Physiol* 1885;9:519-532.

5. Richards AN, Drinker CK. An apparatus for perfusion of isolated organs. *J Pharmacol Exp Ther* 1915;7:467-483.

6. Bayliss LE, Fee AR, Ogden EA. Method of oxygenating blood. *J Physiol* 1928;66:443-448.

7. Daly IB, Thorpe WV. An isolated mammalian heart preparation capable of performing work for long periods. *J Physiol* 1933;79:199-217.

8. Patterson SW, Starling EH. On the mechanical features which determine the output of the ventricles. *J Physiol* 1914;48:357-379

9. Jacob JC. Ein beitrag zur technik der kunstiliechen durchblutung ueberlebender organe. *Arch Exp Pathol Pharmacol* 1895;36:330-348.

10. Brukhonenko S. Tchetchuline S. Experiences avec la tete isolee du chien.1.Technique et conditions des experiences. *J Physiol Pathol Gen* 1929;27:31-45.

11. Brukhonenko S. Circulation artificelle du sang dans l'organisme entire d'un chien avec Coeur exclus. *J Physiol Pathol Gen* 1929;27:257-272.

12. Lillehei CW, Cohen M, Warden HE, et al. The results of direct vision closure of ventricular septal defects in eight patients by means of controlled cross circulation. *Surg Gynecol Obstet* 1955;101:447-466.

13. Lindberg CA. *Autobiography of values.* New York, NY: Harcourt Brace Jovanovich, 1977.

14. Lindbergh CA. An apparatus for the culture of whole organs. *J Exp Med* 1935;62:409-432.

15. Johnson SL. *The History of cardiac surgery, 1896-1955*. Baltimore, MD: Johns Hopkins Press, 1970:121.

16. McLean J. The discovery of heparin. *Circulation* 1959;19:75-78.

17. Letter from Jay McLean to Charles H. Best on November 14, 1940; quoted in Best CH: Preparation of heparin and its use in the first clinical case. *Circulation* 1959;19:79.

18. Howell WH, Holt E. Two new factors in blood coagulation: heparin and pro-antithrombin. *Am J Physiol* 1918;47:328-341.

19. Best C. Preparation of heparin and its use in the first clinical case. *Circulation* 1959;19:79-86.

20. Gibbon JH Jr. The gestation and birth of an idea. *Phila Med* 1963;59:913-916.

21. Gibbon JH Jr. Artificial maintenance of circulation during experimental occlusion of the pulmonary artery. *Arch Surg* 1937;34:1105-1131.

22. Shumacker HB, The birth of an idea and the development of cardiopulmonary bypass. In: Gravlee GP, ed. *Cardiopulmonary bypass and mechanical support: principles and practice*. 3rd ed. Philadelphia, PA: Lippincott, Williams, and Wilkins, 2008:29.

23. Johnson SL. *The History of cardiac surgery, 1896-1955*. Baltimore, MD: Johns Hopkins Press, 1970:145.

24. Johnson SL. *The History of cardiac surgery, 1896-1955*. Baltimore, MD: Johns Hopkins Press, 1970:148.

25. Dennis C, Spreng DS, Nelson GE, et al. Development of a pump oxygenator to replace the heart and lungs: an apparatus applicable to human patients, and application to one case. *Ann Surg* 1951;134:709-721.

26. Digliotti AM. Clinical use of the artificial circulation with a note on intra-arterial transfusion. *Bull Johns Hopkins Hosp* 1951;90:131-133.

27. Dodrill FD, Hill E, Gerisch RA. Temporary mechanical substitute for the left ventricle in man. *JAMA* 1952;150:642-644.

28. Dodrill FD, Hill E, Gerisch RA. Some physiologic aspects of the artificial heart problem. *J Thorac Surg* 1952;24:134-150.

29. Dodrill FD, Hill E, Gerisch RA, et al. Pulmonary valvuloplasty under direct vision using the mechanical heart for a complete bypass of the right heart in a patient with congenital pulmonary stenosis. *J Thorac Surg* 1953;25:584-594.

30. Stephenson LW. The Michigan Heart: first successful open heart operation? Part I. *J Card Surg* 2002;17(3):238-246.

31. Bigelow WG, Callaghan JC, Hopps JA. General hypothermia for experimental intracardiac surgery; the use of electrophrenic respirations, an artificial pacemaker for cardiac standstill and radio-frequency rewarming in general hypothermia. *Am Surg* 1950;132:531-539.

32. Bigelow WG, Lindsay WK, Harrison RC, et al. Oxygen transport and utilization in dogs at low body temperatures. *Am J Physiol* 1950;160:125-137.

33. Bigelow WG, Hopps JA, Callaghan JA. Radiofrequency rewarming in resuscitation from severe hypothermia. *Can J Med Sci* 1952;30:185-193.

34. Bigelow WG. Intellectual humility in medical practice and research. *Surgery* 1969;65(1):1-9.

35. Lewis FJ, Taufic M. Closure of atrial septal defects with the aid of hypothermia: Experimental accomplishments and the report of one successful case. *Surgery* 1953;33:52-59.

36. Swan H, Zeavin I, Blount SG Jr, et al. Surgery by direct vision in the open heart during hypothermia. *JAMA* 1953;153:1081-1085.

37. Hikasa Y, Shirotani H, Satomura K, et al. Open heart surgery in infants with the aid of hypothermic anesthesia. *Arch Jpn Chir* 1967;36:496-508.

38. Horiuchi T, Koyamada K, Matano I, et al. Radical operation for ventricular septal defect in infancy. *J Thorac Cardiovasc Surg* 1963;46:180-190.

39. Dillard DH, Mohri H, Hessel EA II, et al. Correction of total anomalous pulmonary venous drainage in infancy utilizing deep hypothermia with total circulatory arrest. *Circulation* 1967;35(Suppl I):I-105.

40. Wakusawa R, Shibata S, Saito H, et al. Clinical experience in 52 case of open heart surgery under simple profound hypothermia. *Jpn J Anesth* 1968;18:240.

41. Barrett-Boyes BG, Simpson MM, Neutze JM. Intracardiac surgery in neonates and infants using deep hypothermia. *Circulation* 1970;60(Suppl III):III-73.

42. Johnson SL. *The history of cardiac surgery,* 1896-1955. Baltimore, MD: Johns Hopkins Press, 1970:143.

43. Gibbon JH Jr. Application of a mechanical heart and lung apparatus to cardiac surgery. *Minn Med* 1954; 37:171-185.

44. Lillehei CW. Historical development of cardiopulmonary bypass. In: Davis RF, Utley JR, eds. *Cardiopulmonary bypass.* Baltimore, MD: Williams and Wilkins, 1993:1-26.

45. Lillehei CW, Choen M, Warden HE, et al. The direct vision intracardiac correction of congenital anomalies by controlled cross circulation; results in thirty-two patients with ventricular septal defects, tetralogy of Fallot, and atrioventricularis communis defects. *Surgery* 1955; 38:11-29.

46. Kriklin JW, DuShane JW, Patrick RT, et al. Intracardiac surgery with the aid of a mechanical pump-oxygenator system (Gibbon type): report of eight cases. *Proc Staff Meet Mayo Clin* 1955;30:201-206.

47. Kirklin JW. The middle 1950s and C. Walton Lillehei. *J Thorac Cardiovasc Surg* 1989;98:822-824.

48. Spencer FC. Intellectual creativity in thoracic surgeon. *J Thorac Cardiovasc Surg* 1983;86:167-179.

49. Shumacker HB Jr. *The evolution of cardiac surgery*. Bloomington, IN: Indiana University Press, 1992:17.

50. National Academy of Sciences. *Mechanical devices to assist the failing heart: Proceedings of a conference, September 9 & 10, 1964*, Chapters 4-11, pp. 45-143. Washington, DC: National Academy of Sciences, National Research Council. NRC Publication 1283.

51. Johnson SL. *The history of cardiac surgery 1896-1955*. Baltimore, MD: Johns Hopkins, 1970:140-151.

52. Cooley, DA, Development of the roller pump for use in the cardiopulmonary bypass circuit. *Tex Heart Inst J* 1987;14(2):113-118.

53. Tayama E, Raskin SA, Nose Y. Blood pumps (Chapter 3). In: Gravlee G, ed. *Cardiopulmonary bypass: principles and practice*. 2nd ed. Philadelphia, PA: Lippincott Williams, and Wilkins, 2000:37-48.

54. *Centrifugal pump*. Wikipedia May 5, 2015:1-11.

55. Cohn L. *Cardiac surgery in the adult*. 4th ed. New York, NY: McGraw-Hill Companies, 2012:283-329.

56. Dewall RA, Warden HE, Gott VL, et al. Total body perfusion for open cardiotomy utilizing the bubble oxygenator; physiologic responses in man. *J Thorac Surg* 1956;32(5):591-603.

57. Westaby S, Bosher C. Landmarks in cardiac surgery. Oxford, UK: Isis Medical Media Ltd., 1997:64.

58. Lim MW. The history of extracorporeal oxygenators. *Anaesthesia* 2006;61:984-995.

59. Clowens GHA Jr, Neville WE. Further development of a blood oxygenator dependent upon the diffusion of gases through plastic membranes. *Trans Am Soc Artif Intern Organs* 1957;3:52-58.

60. Clowes GHA Jr, Hopkins AL, Neville WE. An artificial lung oxygenator dependent upon diffusion of oxygen and carbon dioxide through plastic membranes. *Thorac Surg* 1956;32:630-637.

61. Drummond M, Braile DM, Lima-Oliveira AM, et al. Technological evolution of membrane oxygenators. *Braz J Cardiovasc Surg* 2005;20(4):432-437.

62. Cohn LH, Virginia MD, Hubbard J. *Cardiac Surgery in the adult*. New York, NY: McGraw Hill Medical, 2012:228.

63. Emmons WO, Sacca DB. The design and development of a blood heat exchanger for open heart surgery. *Gen Motors Eng J* July-September 1958;39.

64. Brown IW, Smith WW, Emmons WO. An efficient blood heat exchanger for use with extracorporeal circulation. *Surgery* 1958;44(2):372-375.

65. Brown IW, Smith WW, Young WG, et al. Experimental and clinical studies of controlled hypothermia