Jay L. Grosfeld
James A. O'Neill, Jr.
Eric W. Fonkalsrud
Arnold G. Coran

PEDIATRIC SURGERY

Sixth Edition

VOLUME 1

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Pediatric Surgery

SIXTH EDITION

VOLUME ONE

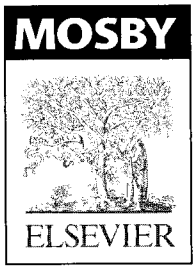
Jay L. Grosfeld, MD
Lafayette Page Professor and Chairman Emeritus
Department of Surgery, Indiana University School of Medicine
Surgeon-in-Chief and Director of Pediatric Surgery Emeritus, Riley Hospital for Children
Indianapolis, Indiana

James A. O'Neill, Jr., MD
John Clinton Foshee Distinguished Professor of Surgery
Former Chairman, Section of Surgical Sciences, Former Chairman, Department of Surgery, Surgeon-in-Chief Emeritus
Vanderbilt University Medical Center
Nashville, Tennessee

Arnold G. Coran, MD
Professor of Pediatric Surgery
University of Michigan Medical School
Former Surgeon-in-Chief
C.S. Mott Children's Hospital
Ann Arbor, Michigan

Eric W. Fonkalsrud, MD
Professor and Emeritus Chief of Pediatric Surgery
David Geffen School of Medicine at UCLA
Department of Surgery
Los Angeles, California

Anthony A. Caldamone, MD, FAAP
Associate Editor, Urology Section
Professor of Surgery (Urology) and Pediatrics
Brown University School of Medicine
Chief of Pediatric Urology, Hasbro Children's Hospital
Providence, Rhode Island



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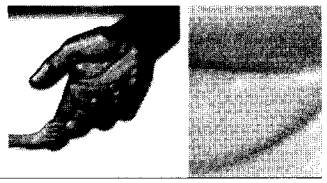
To our wives
Margie, Susan, Peggy, and Susi.
To our children and grandchildren for giving
us the time and providing the sensitivity
and support to prepare these volumes.
To children everywhere who have suffered
from congenital and acquired surgical conditions
and have provided the experience and inspired us.

Contributors



Mark C. Adams, MD, FAAP
Professor of Urology and Pediatrics, Vanderbilt University School of Medicine; Pediatric Urologist, Monroe Carell Jr. Children's Hospital at Vanderbilt, Nashville, Tennessee
Magaureter and Prune-Belly Syndrome

N. Scott Adzick, MD
C. Everett Koop Professor of Pediatric Surgery, University of Pennsylvania School of Medicine; Surgeon-in-Chief, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania
Cysts of the Lungs and Mediastinum

Craig T. Albanese, MD
Professor of Surgery, Pediatrics, and Obstetrics and Gynecology, and Chief, Division of Pediatric Surgery, Department of Surgery, Stanford Hospital & Clinics, Stanford; John A. and Cynthia Fry Gunn Director of Surgical Services, Lucile Packard Children's Hospital at Stanford, Palo Alto, California
Necrotizing Enterocolitis

Fred Alexander, MD
Associate Professor of Surgery, Cleveland Clinic Lerner School of Medicine of Case Western Reserve University; Staff Surgeon, Cleveland Clinic Foundation, Cleveland, Ohio
Crohn's Disease

R. Peter Altman, MD
Professor of Surgery, Columbia University College of Physicians and Surgeons; Surgeon-in-Chief, Morgan Stanley Children's Hospital of New York Presbyterian, New York, New York
The Jaundiced Infant: Biliary Atresia

Richard J. Andrassy, MD
Denton A. Cooley Professor and Chairman, Department of Surgery, University of Texas Medical School at Houston; Executive Vice President of Clinical Affairs and Associate Dean for Clinical Affairs, University of Texas at Houston, Houston, Texas
Rhabdomyosarcoma

Walter S. Andrews, MD
Professor of Surgery, University of Missouri–Kansas City School of Medicine; Director, Transplantation Program, Children's Mercy Hospital, Kansas City, Missouri
Gallbladder Disease and Hepatic Infections

Harry Applebaum, MD
Clinical Professor of Surgery, David Geffen School of Medicine at UCLA; Head, Division of Pediatric Surgery, Kaiser Permanente Medical Center, Los Angeles, California
Duodenal Atresia and Stenosis—Annular Pancreas

Marjorie J. Arca, MD
Assistant Professor of Surgery, Medical College of Wisconsin; Attending Surgeon, Children's Hospital of Wisconsin, Milwaukee, Wisconsin
Atresia, Stenosis, and Other Obstructions of the Colon

Robert M. Arensman, MD
Professor of Surgery, Louisiana State University School of Medicine; Attending Surgeon, Ochsner Clinic Foundation, New Orleans, Louisiana
Gastrointestinal Bleeding

James B. Atkinson, MD
Professor and Chief, Division of Pediatric Surgery, Department of Surgery, David Geffen School of Medicine at UCLA, Los Angeles, California
Liver Tumors

Richard G. Azizkhan, MD, PhD(Hon)
Professor of Surgery and Pediatrics, Lester Martin Chair of Pediatric Surgery, and Vice Chair, Department of Surgery, University of Cincinnati College of Medicine; Surgeon-in-Chief and Director, Division of Pediatric Surgery, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio
Teratomas and Other Germ Cell Tumors

Anwar Baban, MD
Laboratory of Molecular Genetics, Gaslini Children's Hospital, Genoa, Italy
Hirschsprung's Disease and Related Neuromuscular Disorders of the Intestine

Douglas C. Barnhart, MD, MSPH
Assistant Professor, Departments of Surgery and Pediatrics, University of Alabama at Birmingham School of Medicine; Attending Surgeon, The Children's Hospital of Alabama, Birmingham, Alabama
Biopsy Techniques for Children with Cancer

Robert H. Bartlett, MD
Professor of Surgery, University of Michigan Medical School, Ann Arbor, Michigan
Extracorporeal Life Support for Cardiopulmonary Failure

Laurence S. Baskin, MD
Professor of Urology, University of California, San Francisco, School of Medicine; Chief, Pediatric Urology, UCSF Children's Hospital at UCSF Medical Center, San Francisco, California
Hypospadias

Spencer W. Beasley, MB, ChB, MS
Clinical Professor of Pediatrics and Surgery, Christchurch School of Medicine and Health Sciences, University of Otago; Chief of Child Health Services, Division of Child Health, and Clinical Director, Paediatric Surgery, Christchurch Hospital, Christchurch, New Zealand
Torticollis

Michael L. Bentz, MD, FAAP, FACS
Professor of Surgery, Pediatrics, and Plastic Surgery, and Chairman, Division of Plastic Surgery, University of Wisconsin School of Medicine and Public Health; Chief of Plastic Surgery, University of Wisconsin Hospital and Clinics, Madison, Wisconsin
Hand, Soft Tissue, and Envenomation Injuries

Victor E. Boston, MD, FRCSI, FRCSEng, FRCSEd
Honorary Senior Lecturer, Department of Surgery, The Queen's University of Belfast Faculty of Medicine; The Royal Belfast Hospital for Sick Children, Belfast, Northern Ireland
Ureteral Duplication and Ureteroceles

Scott C. Boulanger, MD, PhD
Assistant Professor of Surgery, Division of Pediatric Surgery, University of Mississippi Medical Center School of Medicine, Jackson, Mississippi
Inguinal Hernias and Hydroceles

Edward L. Bove, MD
Professor of Surgery, University of Michigan Medical School; Head, Section of Cardiac Surgery, C.S. Mott Children's Hospital, Ann Arbor, Michigan
Congenital Heart Disease and Anomalies of the Great Vessels

Mary L. Brandt, MD
Professor and Vice Chair, Michael E. DeBakey Department of Surgery, Baylor College of Medicine, Texas Children's Hospital, Houston, Texas
Disorders of the Breast

John W. Brock III, MD
Professor of Urologic Surgery, Vanderbilt University School of Medicine; Director, Pediatric Urology, Vanderbilt Medical Center; Surgeon in Chief, Monroe Carell Jr. Children's Hospital at Vanderbilt, Nashville, Tennessee
Bladder Exstrophy

Rebeccah L. Brown, MD
Assistant Professor of Clinical Surgery and Pediatrics, University of Cincinnati College of Medicine; Associate Director of Trauma Services, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio
Genitourinary Tract Trauma

Marybeth Browne, MD
Surgical Resident, McGaw Medical Center of Northwestern University, Chicago, Illinois
Gastrointestinal Bleeding

Terry L. Buchmiller, MD
Formerly Assistant Professor of Surgery, Weill Medical College of Cornell University of New York, New York; Currently Assistant Professor of Surgery, Harvard Medical School; Assistant in Surgery, Children's Hospital Boston, Boston, Massachusetts
The Jaundiced Infant: Biliary Atresia

Ronald W. Busuttil, MD, PhD
Professor and Executive Chairman, Department of Surgery, David Geffen School of Medicine at UCLA; Chief, Division of Liver and Pancreas Transplantation, Dumont-UCLA Liver Cancer Center; Director, Pfleger Liver Institute, UCLA Medical Center, Los Angeles, California
Liver Transplantation

Michelle S. Caird, MD
Lecturer, Department of Orthopaedic Surgery, Alfred Taubman Health Care Center, University of Michigan, Ann Arbor, Michigan
Musculoskeletal Trauma

Anthony A. Caldamone, MD, FAAP
Professor of Surgery (Urology) and Pediatrics, Brown University School of Medicine; Chief of Pediatric Urology, Hasbro Children's Hospital, Providence, Rhode Island
Renal Infection, Abscess, Vesicoureteral Reflux, Urinary Lithiasis, and Renal Vein Thrombosis

Darrell A. Campbell, Jr., MD
Professor of Surgery, University of Michigan Medical School; Chief of Clinical Affairs, University of Michigan Health System, Ann Arbor, Michigan
Renal Transplantation

Donna A. Caniano, MD
Professor of Surgery and Pediatrics, The Ohio State University College of Medicine and Public Health; Surgeon-in-Chief, Children's Hospital, Columbus, Ohio
Ethical Considerations

Michael G. Caty, MD
Associate Professor of Surgery and Pediatrics, University at Buffalo School of Medicine and Biomedical Science; Surgeon-in-Chief, Women and Children's Hospital of Buffalo, Buffalo, New York
Adrenal Tumors

Dai H. Chung, MD
Associate Professor of Surgery and Pediatrics, The University of Texas Medical Branch School of Medicine at Galveston; Chief, Section of Pediatric Surgery, UTMB Children's Hospital, Galveston, Texas
Burns

Robert E. Cilley, MD
Professor of Surgery and Pediatrics, Penn State College of Medicine; Chief, Division of Pediatric Surgery, Milton S. Hershey Medical Center, Hershey, Pennsylvania
Disorders of the Umbilicus

Paul M. Colombani, MD
Professor of Surgery, Pediatrics, and Oncology, and Robert Garrett Professor of Surgery, Johns Hopkins University School of Medicine; Chief, Division of Pediatric Surgery, Johns Hopkins Medicine; Pediatric Surgeon-in-Charge, Johns Hopkins Hospital, Baltimore, Maryland
Surgical Implications Associated with Bone Marrow Transplantation

Joel D. Cooper, MD
Professor of Surgery, University of Pennsylvania School of Medicine; Chief, Division of Thoracic Surgery, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania
Lung Transplantation

Arnold G. Coran, MD
Professor of Pediatric Surgery, University of Michigan Medical School, Ann Arbor, Michigan
Nutritional Support; Congenital Anomalies of the Esophagus; Hirschsprung's Disease and Related Neuromuscular Disorders of the Intestine; Abnormalities of the Female Genital Tract

Robin T. Cotton, MD
Professor of Otolaryngology, University of Cincinnati School of Medicine; Director, Pediatric Otolaryngology–HNS, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio
Lesions of the Larynx, Trachea, and Upper Airway

Michael C. Dalsing, MD
Professor of Surgery and Director, Section of Vascular Surgery, Indiana University School of Medicine, Indianapolis, Indiana
Venous Disorders in Childhood

Alan Daneman, MBBCh, BSc, FRANZCR, FRCPC
Professor of Radiology, University of Toronto Faculty of Medicine; Staff Radiologist, Hospital for Sick Children, Toronto, Ontario, Canada
Intussusception

Andrew M. Davidoff, MD
Associate Professor, Department of Surgery and Pediatrics, University of Tennessee School of Medicine; Chief, Division of General Pediatric Surgery, St. Jude Children's Research Hospital, Memphis, Tennessee
Principles of Pediatric Oncology, Genetics of Cancer, and Radiation Therapy

Richard S. Davidson, MD
Associate Professor, University of Pennsylvania School of Medicine; Attending Surgeon, Children's Hospital of Philadelphia and Shrener's Hospital, Philadelphia
Musculoskeletal Trauma

Romano T. DeMarco, MD
Assistant Professor of Urologic Surgery, Division of Pediatric Urology, Vanderbilt University School of Medicine, Nashville, Tennessee
Bladder Exstrophy

Daniel A. DeUgarte, MD
Pediatric Surgery Fellow, University of Michigan Medical School and C.S. Mott Children's Hospital, Ann Arbor, Michigan
Liver Tumors

Eric Devaney, MD
Assistant Professor of Surgery, University of Michigan Medical School; Attending Surgeon, C.S. Mott Children's Hospital, Ann Arbor, Michigan
Congenital Heart Disease and Anomalies of the Great Vessels

William Didelot, MD
Professor of Pediatric Orthopaedics, Indiana University School of Medicine; Staff Surgeon, Riley Hospital for Children, Indianapolis, Indiana
Major Congenital Orthopedic Deformitites

John W. DiFiore, MD
Clinical Assistant Professor of Surgery, Case School of Medicine; Staff Pediatric Surgeon, Children's Hospital at Cleveland Clinic, Cleveland, Ohio
Respiratory Physiology and Care

Patrick A. Dillon, MD
Assistant Professor of Surgery, Washington University in St. Louis School of Medicine; Attending Surgeon, St. Louis Children's Hospital, St. Louis, Missouri
Gastrointestinal Tumors

Peter W. Dillon, MD
Professor of Surgery and Pediatrics, Penn State College of Medicine; Vice Chair, Department of Surgery, and Chief, Division of Pediatric Surgery, Penn State Children's Hospital, Hershey, Pennsylvania
Congenital Diaphragmatic Hernia and Eventration

Patricia K. Donahoe, MD
Marshall K. Bartlett Professor of Surgery, Harvard Medical School; Director, Pediatric Surgical Research Laboratories and Chief, Pediatric Surgical Services Emerita, Massachusetts General Hospital, Boston
Ambiguous Genitalia

James C. Y. Dunn, MD, PhD
Assistant Professor of Surgery, David Geffen School of Medicine at UCLA; Attending Surgeon, Mattel Children's Hospital at UCLA, Los Angeles, California
Appendicitis

Simon Eaton, BSc, PhD
Senior Lecturer in Pediatric Surgery and Metabolic Biochemistry, Department of Pediatric Surgery, Institute of Child Health, University College London, London, United Kingdom
Neonatal Physiology and Metabolic Considerations

Martin R. Eichelberger, MD
Professor of Surgery and Pediatrics, George Washington University School of Medicine and Health Sciences; Director, Emergency Trauma, Burn Service, and Senior Attending, Pediatric Surgery Service, Children's National Medical Center; President and CEO, Safe Kids Worldwide, Washington, DC
Accident Victims and Their Emergency Management

Sigmund H. Ein, MDCM, FRCSC, FAAP, FACS
Associate Professor of Surgery, Adjunct Clinical Faculty, Department of Surgery, University of Toronto Faculty of Medicine; Honorary Staff Surgeon, Division of General Surgery, The Hospital for Sick Children, Toronto; Courtesy Staff, Department of Surgery, Lakeridge Health Corporation, Oshawa, Ontario, Canada
Intussusception

Carolyn Ells, RTT, PhD
Assistant Professor of Medicine, McGill University Faculty of Medicine; Clinical Ethicist, Sir Mortimer B. Davis Jewish General Hospital, Montreal, Quebec, Canada
Ethical Considerations

Barry L. Eppley, MD, DMD
Professor of Plastic Surgery, Indiana University School of Medicine, Indianapolis, Indiana
Cleft Lip and Palate

Mary E. Fallat, MD
Professor of Surgery, and Director, Division of Pediatric Surgery, University of Louisville; Chief of Surgery, Kosdir Children's Hospital, Louisville, Kentucky
Ovarian Tumors

Diana L. Farmer, MD
Professor of Clinical Surgery, Pediatrics and Obstetrics, Gynecology, and Reproductive Medicine, University of California, San Francisco, School of Medicine; Surgeon-in-Chief, UCSF Children's Hospital, San Francisco, California
Cysts of the Lungs and Mediastinum

Douglas G. Farmer, MD
Associate Professor of Surgery, David Geffen School of Medicine at UCLA; Director, Intestinal Transplantation, Dumont-UCLA Transplant Center, Los Angeles, California
Liver Transplantation; Intestinal Transplantation

Steven J. Fishman, MD
Professor of Surgery, Harvard University Medical School; Senior Associate in Surgery, Children's Hospital Boston, Boston, Massachusetts
Vascular Anomalies: Hemangiomas and Malformations

Alan W. Flake, MD
Professor of Surgery and Obstetrics and Gynecology, University of Pennsylvania School of Medicine; Director, Children's Institute for Surgical Science, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania
Molecular Clinical Genetics and Gene Therapy

Robert P. Foglia, MD
Associate Professor of Surgery and Division Chief, Pediatric Surgery, Washington University in St. Louis School of Medicine; Surgeon-in-Chief, St. Louis Children's Hospital, St. Louis, Missouri
Gastrointestinal Tumors

Eric W. Fonkalsrud, MD
Professor of Surgery, David Geffen School of Medicine at UCLA; Emeritus Chief of Pediatric Surgery, UCLA Medical Center, Los Angeles, California
Ulcerative Colitis; Lymphatic Disorders

Henri R. Ford, MD
Vice-Chair and Visiting Professor of Surgery, Keck School of Medicine of USC; Surgeon-in-Chief and Vice President, Surgery, and Medical Director, Burtie Green Bettingen Surgery Center, Children's Hospital Los Angeles, Los Angeles, California
Sepsis and Related Considerations

Stephanie M. P. Fuller, MD
Clinical Fellow, Division of Cardiothoracic Surgery, The Children's Hospital of Philadelphia and Thomas Jefferson University Hospital, Philadelphia, Pennsylvania
Heart Transplantation

Victor F. Garcia, MD
Professor of Surgery, University of Cincinnati College of Medicine; Director of Trauma Services, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio
Genitourinary Tract Trauma; Bariatric Surgery in Adolescents

John M. Gatti, MD
Assistant Professor of Surgery and Urology, University of Missouri–Kansas City School of Medicine; Director of Minimally Invasive Urology, Children's Mercy Hospital of Kansas City, Kansas City, Missouri
Abnormalities of the Urethra, Penis, and Scrotum

Michael W. L. Gauderer, MD
Professor of Surgery and Pediatrics (Greenville), University of South Carolina School of Medicine, Columbia; Adjunct Professor of Bioengineering, Clemson University, Clemson; Chief, Division of Pediatric Surgery, Children's Hospital, Greenville Hospital System, Greenville, South Carolina
Stomas of the Small and Large Intestine

James D. Geiger, MD
Associate Professor of Surgery, University of Michigan Medical School; Staff Surgeon, C.S. Mott Children's Hospital, Ann Arbor, Michigan
Biopsy Techniques for Children with Cancer

Keith E. Georgeson, MD
Professor of Surgery, University of Alabama at Birmingham School of Medicine; Chief of Pediatric Surgery, The Children's Hospital of Alabama, Birmingham, Alabama
Gastroesophageal Reflux Disease

Cynthia A. Gingalewski, MD
Assistant Professor of Surgery and Pediatrics, George Washington University School of Medicine and Health Science; Pediatric Surgeon, Children's National Medical Center, Washington, DC
Other Causes of Intestinal Obstruction

Kenneth I. Glassberg, MD
Professor of Urology, Columbia University College of Physicians and Surgeons; Director, Division of Pediatric Urology, Morgan Stanley Children's Hospital of New York–Presbyterian, New York, New York
Renal Agenesis, Dysplasia, and Cystic Disease

Philip L. Glick, MD, MBA
Professor of Surgery, Pediatrics, and Obstetrics and Gynecology, University of Buffalo School of Medicine and Biomedical Sciences; Executive Director, Miniature Access Surgery Center (MASC), Women and Children's Hospital of Buffalo, Buffalo, New York
Inguinal Hernias and Hydroceles

Sherilyn A. Gordon, MD
Assistant Professor of Surgery, Division of Liver and Pancreas Transplantation, David Geffen School of Medicine at UCLA, Los Angeles, California
Intestinal Transplantation

Tracy C. Grikscheit, MD
Senior Fellow in Pediatric Surgery, Children's Hospital and Regional Medical Center and University of Washington School of Medicine, Seattle, Washington
The Impact of Tissue Engineering in Pediatric Surgery

Jay L. Grosfeld, MD
Lafayette Page Professor of Pediatric Surgery Emeritus, Indiana University School of Medicine; Surgeon-in-Chief Emeritus, Riley Hospital for Children, Indianapolis, Indiana
Neuroblastoma; Jejunoileal Atresia and Stenosis; Abnormalities of the Female Genital Tract

Angelika C. Gruessner, MS, PhD
Associate Professor of Surgical Science, University of Minnesota Medical School, Minneapolis, Minnesota
Pancreas and Islet Cell Transplantation

Rainer W. G. Gruessner
Professor of Surgery, University of Minnesota Medical School, Minneapolis, Minnesota
Pancreas and Islet Cell Transplantation

Philip C. Guzzetta, Jr., MD
Professor of Surgery and Pediatrics, George Washington University School of Medicine and Health Sciences; Interim Chief of Pediatric Surgery, Children's National Medical Center, Washington, DC
Nonmalignant Tumors of the Liver

Carroll M. Harmon, MD, PhD,
Associate Professor of Surgery, University of Alabama at Birmingham School of Medicine; Attending Surgeon, Children's Hospital, Birmingham, Alabama
Congenital Anomalies of the Esophagus

Michael R. Harrison, MD
Professor of Surgery, Pediatrics, and Obstetrics, Gynecology, and Reproductive Sciences, University of California, San Francisco, School of Medicine; Director, Fetal Treatment Center, UCSF Children's Hospital and Medical Center, San Francisco, California
The Fetus as a Patient

Andrea A. Hayes-Jordan, MD
Assistant Professor of Surgery and Pediatrics, University of Texas Medical School at Houston and M.D. Anderson Cancer Center; Pediatric Surgeon, Memorial Hermann Children's Hospital and M.D. Anderson Cancer Center, Houston, Texas
Lymph Node Disorders

Stephen R. Hays, MD, MS, FAAP
Assistant Professor of Anesthesiology and Pediatrics, Vanderbilt University School of Medicine; Director, Pediatric Pain Services, Vanderbilt Children's Hospital, Nashville, Tennessee
Pediatric Anesthesia

John H. Healey, MD
Professor of Orthopaedic Surgery, Weill Medical College of Cornell University; Chief of Orthopaedic Surgery, Memorial Sloan-Kettering Cancer Center, New York, New York
Bone Tumors

W. Hardy Hendren III, MD, FACS, FAAP, FRCS (Irel&Engl), FRCPS(Glasgow), DSc(Drexel), MD(HonCausa) Université Aix Marseilles
Robert E. Gross Distinguished Professor of Surgery, Harvard Medical School; Chief of Surgery Emeritus, Children's Hospital Boston; Honorary Surgeon, Massachusetts General Hospital, Boston, Massachusetts
Megaureter and Prune-Belly Syndrome

Bernhard J. Hering, MD
Assistant Professor of Surgery, University of Minnesota Medical School; Associate Director, Diabetes Institute for Immunology and Transplantation, University of Minnesota Medical Center, Fairview, Minneapolis, Minnesota
Pancreas and Islet Cell Tranplantation

David N. Herndon, MD
Professor of Surgery and Pediatrics and Jesse H. Jones Distinguished Chair in Burn Surgery, University of Texas Medical Branch School of Medicine at Galveston; Chief of Staff and Director of Research, Shriners Burns Hospital, Galveston, Texas
Burns

Ronald B. Hirschl, MD
Professor of Surgery, University of Michigan Medical School; Head, Section of Pediatric Surgery, and Surgeon-in-Chief, C.S. Mott Children's Hospital, Ann Arbor, Michigan
Extracorporeal Life Support for Cardiopulmonary Failure

George W. Holcomb III, MD, MBA
Katharine Berry Richardson Professor of Surgery, University of Missouri–Kansas City School of Medicine; Surgeon-in-Chief, Children's Mercy Hospital, Kansas City, Missouri
Gallbladder Disease amd Hepatic Infections

Charles B. Huddleston, MD
Professor of Surgery, Washington University in St. Louis School of Medicine; Chief, Pediatric Cardiothoracic Surgery, and Surgical Director, Lung Transplant Program, St. Louis Children's Hospital, St. Louis, Missouri
Lung Transplantation

Raymond J. Hutchinson, MS, MD
Professor of Pediatrics, University of Michigan Medical School; Director of Clinical Services, Pediatric Hematology/Oncology, C.S. Mott Children's Hospital, Ann Arbor, Michigan
Surgical Implications of Hematologic Disease

John M. Hutson, MD(Monash), MD(Melb), FRACS, FAAP(Hon)
Professor of Pediatric Surgery, Department of Pediatrics, University of Melbourne Faculty of Medicine, Melbourne; Director of General Surgery, Royal Children's Hospital, Parkville, Victoria, Australia
Undescended Testis, Torsion, and Varicocele

Thomas Inge, MD, PhD
Associate Professor of Surgery and Pediatrics, University of Cincinnati College of Medicine; Surgical Director, Comprehensive Weight Management Program, Cincinnati Children's Hospital Medical Center, Cincinnati
Bariatric Surgery in Adolescents

Vincenzo Jasonni, MD
Professor of Pediatric Surgery, University of Genoa Medical School; Surgeon-in-Chief and Chair of Pediatric Surgery, Gaslini Children's Hospital, Genoa, Italy
Hirschsprung's Disease and Related Neuromuscular Disorders of the Intestine

Nishwan Jibri, MD
Department of Pediatric Surgery, Gaslini Children's Hospital, Genoa, Italy
Hirschsprung's Disease and Related Neuromuscular Disorders of the Intestine

Byron D. Joyner, MD
Associate Professor of Urology, University of Washington School of Medicine; Residency Director, University of Washington Urology Program, and Faculty/Staff, Children's Hospital and Regional Medical Center, Seattle, Washington
Ureteropelvic Junction Obstruction

Martin Kaefer, MD
Associate Professor, Department of Urology, Indiana University School of Medicine; Pediatric Urologist, Riley Children's Hospital, Indianapolis, Indiana
Disorders of Bladder Function

Henry K. Kawamoto, Jr., MD, DDS
Clinical Professor of Surgery, Department of Surgery, Division of Plastic Surgery, David Geffen School of Medicine at UCLA; Director, Craniofacial Surgery, UCLA Medical Center, Los Angeles, California
Craniofacial Anomalies

Robert M. Kay, MD
Associate Professor of Orthopedic Surgery, Keck School of Medicine of USC; Orthopedic Surgeon, Children's Hospital Los Angeles, Los Angeles, California
Bone and Joint Infections

Kosmas Kayes, MD
Staff Surgeon, Riley Hospital for Children and St. Vincent Children's Hospital, Indianapolis, Indiana
Major Congenital Orthopedic Deformities

Mark L. Kayton, MD
Assistant Member, Memorial Sloan-Kettering Cancer Center; Assistant Attending Surgeon, Division of Pediatric Surgery, Memorial Hospital, New York, New York
Surgical Implications Associated with Bone Marrow Transplantation

Robert E. Kelly, Jr., MD, FACS, FAAP
Associate Professor of Clinical Surgery and Pediatrics, Eastern Virginia Medical School, Children's Hospital of the King's Daughters, Norfolk, Virginia
The Nuss Procedure for Pectus Excavatum [Chapter 59]

Stephen S. Kim, MD
Assistant Professor of Surgery, University of Washington School of Medicine; Attending, Division of Pediatric Surgery, Children's Hospital and Regional Medical Center, Seattle, Washington
Necrotizing Enterocolitis

Michael D. Klein, MD
Arvin I. Philippart Chair and Professor of Surgery, Wayne State University School of Medicine; Surgeon-in-Chief, Children's Hospital of Michigan, Detroit, Michigan
Congenital Defects of the Abdominal Wall

Giannoula Klement, MD
Instructor in Pediatrics (Hematology-Oncology), Harvard University Medical School; Assistant in Pediatrics, Children's Hospital Boston, Boston, Massachusetts
Vascular Anomalies: Hemangiomas and Malformations

Matthew J. Krasin, MD
Assistant Member and Radiation Oncologist, St. Jude Children's Research Hospital, Memphis, Tennessee
Principles of Pediatric Oncology, Genetics of Cancer, and Radiation Therapy

Thomas M. Krummel, MD, FACS
Professor in Surgery, Stanford University School of Medicine; Service Chief, Surgery, Stanford Hospital & Clinics, Stanford; Susan B. Ford Surgeon-in-Chief, Lucile Packard Children's Hospital at Stanford, Palo Alto, California
New and Emerging Surgical Technologies and the Process of Innovation

Jean-Martin Laberge, MD, FRCSC, FACS
Professor of Surgery, McGill University Faculty of Medicine; Director, Division of Pediatric General Surgery, The Montreal Children's Hospital, Montreal, Quebec, Canada
Infections and Diseases of the Lungs, Pleura, and Mediastinum

Ira S. Landsman, MD
Associate Professor of Anesthesiology and Pediatrics, Vanderbilt University School of Medicine; Director, Division of Pediatric Anesthesia, Vanderbilt Children's Hospital, Nashville, Tennessee
Pediatric Anesthesia

Michael P. La Quaglia, MD
Professor of Surgery, Weill Medical College of Cornell University; Chief, Pediatric Surgical Service, Memorial Sloan-Kettering Cancer Center, New York, New York
Hodgkin's Disease and Non-Hodgkin's Lymphoma

Stanley T. Lau, MD
Pediatric Surgery Fellow, Women and Children's Hospital of Buffalo, Buffalo, New York
Adrenal Tumors

Steven L. Lee, MD
Regional Pediatric Surgeon, Kaiser Permanente, Los Angeles Medical Center, Los Angeles, California
Duodenal Atresia and Stenosis—Annular Pancreas

Joseph L. Lelli, Jr., MD
Assistant Professor of Surgery, Wayne State Medical School; Pediatric Surgeon, The Children's Hospital of Michigan, Detroit, Michigan
Polypoid Diseases of the Gastrointestinal Tract

Marc A. Levitt, MD
Assistant Professor of Surgery and Pediatrics, University of Cincinnati College of Medicine; Associate Director, Colorectal Center for Children, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio
Anorectal Malformations

Harry Lindahl, MD, PhD
Lecturer in Pediatrics, University of Helsinki School of Medicine; Chief of Pediatric Surgery, Hospital for Children and Adolescents, Helsinki; University Central Hospital, Helsinki, Finland
Esophagoscopy and Diagnostic Techniques

Thom E. Lobe, MD
Professor of Surgery and Pediatrics, University of Tennessee School of Medicine, Memphis, Tennessee; Pediatric Surgeon, Blank Children's Hospital, Des Moines, Iowa
Other Soft Tissue Tumors

Randall T. Loder, MD
Garceau Professor of Orthopaedic Surgery, Indiana University School of Medicine; Director of Pediatric Orthopaedics, Riley Hospital for Children, Indianapolis, Indiana
Amputations in Children

Thomas G. Luerssen, MD
Professor of Neurological Surgery, Indiana University School of Medicine; Chief, Pediatric Neurosurgery Service, Riley Hospital for Children, Indianapolis, Indiana
Central Nervous System Injuries

Jeffrey R. Lukish, MD
Associate Professor of Surgery and Pediatrics, Uniformed Services University of the Health Sciences F. Edward Hébert School of Medicine, Bethesda, Maryland; Chief, Division of Pediatric Surgery, and Attending Pediatric Surgeon, The National Naval Medical Center and Walter Reed Army Medical Center, Washington, DC
Accident Victims and Their Emergency Management

Dennis P. Lund, MD
Chairman, Division of General Surgery, University of Wisconsin-Madison, and Surgeon-in-Chief, UW Children's Hospital, Madison, Wisconsin
Alimentary Tract Duplications

Mary Beth Madonna, MD
Assistant Professor of Surgery, Northwestern University Feinberg School of Medicine; Attending Surgeon, Children's Memorial Hospital and John H. Stroger, Jr. Hospital of Cook County, Chicago, Illinois
Gastrointestinal Bleeding

John C. Magee, MD
Associate Professor of Surgery, University of Michigan Medical School; Director, Adult and Pediatric Renal Transplantation, and Director, Pediatric Liver Transplantation, University of Michigan Health System, Ann Arbor, Michigan
Renal Transplantation

Giuseppe Martucciello, MD
Associate Professor of Pediatric Surgery, Faculty of Medicine, University of Genoa, Genoa, and University of Pavia, Pavia; Director, and Surgeon-in-Chief, Department of Pediatric Surgery, IRCCS Scientific Institute Policlinico San Matteo, Pavia, Italy
Hirschsprung's Disease and Related Neuromuscular Disorders of the Intestine

Stephen J. Mathes, MD
Professor of Surgery and Head, Division of Plastic and Reconstructive Surgery, University of California, San Francisco, School of Medicine, San Francisco, California
Congenital Defects of the Skin, Connective Tissues, Muscles, Tendons, and Hands

Eugene D. McGahren III, MD
Associate Professor of Surgery and Pediatrics, University of Virginia School of Medicine; Pediatric Surgeon, University of Virginia Health System, Charlottesville, Virginia
Laryngoscopy, Bronchoscopy, and Thoracoscopy; Ascites

Leslie T. McQuiston, MD, FAAP
Staff Pediatric Urologist, Urology Associates of North Texas, Cook Children's Hospital, Fort Worth, Texas
Renal Infection, Abscess, Vesicoureteral Reflux, Urinary Lithiasis, and Renal Vein Thrombosis

Peter Metcalfe, MD, FRCSC
Pediatric Urology Fellow, Indiana University School of Medicine and Riley Hospital for Children, Indianapolis, Indiana
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Alastair J. W. Millar, MBChB(Cape Town), FRCS, FRACS, FCS(SA), DCh
Honorary Professor, Paediatric Transplantation and Hepatopancreaticobiliary Surgery, University of Birmingham; Consultant, Paediatric Liver and Intestinal Transplantation and Hepatopancreaticobiliary Surgery, Birmingham Children's Hospital, Birmingham, United Kingdom
Caustic Strictures of the Esophagus

Eugene Minevich, MD, FACS, FAAP
Assistant Professor of Surgery, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio
Structural Disorders of the Bladder, Augmentation

Edward P. Miranda, MD
Professor of Surgery, Division of Plastic Surgery, University of California, San Francisco, School of Medicine, San Francisco, California
Congenital Defects of the Skin, Connective Tissues, Muscles, Tendons, and Hands

Michael E. Mitchell, MD
Professor of Urology, University of Washington School of Medicine; Chief, Pediatric Urology, Children's Hospital and Regional Medical Center, Seattle, Washington
Ureteropelvic Junction Obstruction

Takeshi Miyano, MD, PhD
Professor, Department of Pediatric Surgery, Juntendo University School of Medicine; Director, Juntendo University Hospital, Tokyo, Japan
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Delora Mount, MD, FACS, FAAP
Assistant Professor of Surgery and Pediatrics, University of Wisconsin School of Medicine and Public Health; Chief of Pediatric Plastic Surgery, University of Wisconsin Hospital and Clinics; Director, Craniofacial Anomalies Clinic, American Family Children's Hospital, Madison, Wisconsin
Hand, Soft Tissue, and Envenomation Injuries

Pierre Mouriquand, MD
Professor of Pediatric Urology, Claude-Bernard University Medical School; Head, Department of Pediatric Urology, Debrousse Hospital, Lyon, France
Renal Fusions and Ectopia

Noriko Murase, MD
Associate Professor of Surgery, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania
Principles of Transplantation

J. Patrick Murphy, MD
Professor of Surgery, University of Missouri–Kansas City School of Medicine; Chief, Urology Section, Children's Mercy Hospital of Kansas City, Kansas City, Missouri
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Saminathan S. Nathan, MD
Director, Musculoskeletal Oncology Service, Department of Orthopaedics, National University Hospital, Singapore, Singapore
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Kurt D. Newman, MD
Professor of Surgery and Pediatrics, George Washington University School of Medicine and Health Sciences; Surgeon-in-Chief, Children's National Medical Center; Executive Director, Joseph E. Robert, Jr. Center for Surgical Care, Washington, DC
Lymph Node Disorders

Alp Numanoglu, MD, FCS(SA)
Senior Lecturer in Paediatric Surgery, University of Cape Town School of Child and Adolescent Health; Senior Specialist, Department of Paediatric Surgery, Red Cross Children's Hospital, Institute of Child Health, Cape Town, South Africa
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Donald Nuss, MB, ChB, FRCS(C), FACS, FAAP
Professor of Clinical Surgery and Pediatrics, Eastern Virginia Medical School; Children's Hospital of the King's Daughters, Norfolk, Virginia
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Richard Ohye, MD
Assistant Professor of Surgery, University of Michigan Medical School; Surgical Director, Pediatric Cardiac Transplantation, and Director, Pediatric Cardiovascular Surgery Fellowship Program, C.S. Mott Children's Hospital, Ann Arbor, Michigan
Congenital Heart Disease and Anomalies of the Great Vessels

Keith T. Oldham, MD
Professor of Surgery, Medical College of Wisconsin; Surgeon-in-Chief, Children's Hospital of Wisconsin, Milwaukee, Wisconsin
Atresia, Stenosis, and Other Obstructions of the Colon

James A. O'Neill, Jr., MD, MA(Hon)
J.C. Foshee Professor and Chairman Emeritus, Section of Surgical Sciences, Vanderbilt University School of Medicine; Surgeon-in-Chief Emeritus, Vanderbilt University Medical Center, Nashville, Tennessee
Choledochal Cyst; Bladder and Cloacal Exstrophy; Conjoined Twins; Arterial Disorders

Evelyn Ong, MBBS, BSc, FRCS(Eng)
Joint Royal College of Surgeons of England/British Association of Paediatric Surgeons Research Fellow; Department of Paediatric Surgery, Institute of Child Health, University College London; Clinical Research Fellow, Great Ormond Street Hospital for Children NHS Trust, London, United Kingdom
Neonatal Physiology and Metabolic Considerations

William L. Oppenheim, MD
Professor of Orthopedic Surgery, David Geffen School of Medicine at UCLA; Director of Pediatric Orthopedics, UCLA Medical Center; Consultant, Shriners Hospital of Los Angeles, Los Angeles, California
Bone and Joint Infections

H. Biemann Othersen, Jr., MD
Professor of Surgery and Pediatrics and Emeritus Head, Division of Pediatric Surgery, Medical University of South Carolina College of Medicine; Attending Surgeon, MUSC Children's Hospital, Charleston, South Carolina
Wilms' Tumor

Mikki Pakarinen, MD, PhD
Consultant Pediatric Surgeon, Hospital for Children and Adolescents, University of Helsinki Medical Faculty, Helsinki, Finland
Other Disorders of the Anus and Rectum, Anorectal Function

Keshav Pandurangi, MD
Vascular Surgery Fellow, Indiana University School of Medicine, Indianapolis, Indiana
Venous Disorders in Childhood

Richard H. Pearl, MD, FACS, FAAP, FRCSC
Professor of Surgery and Pediatrics,University of Illinois College of Medicine at Peoria; Surgeon-in-Chief, Children's Hospital of Illinois, Peoria, Illinois
Abdominal Trauma

Alberto Peña, MD
Professor of Surgery and Pediatrics, University of Cincinnati College of Medicine; Director, Colorectal Center for Children, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio
Anorectal Malformations

Rafael V. Pieretti, MD
Chief, Section of Pediatric Urology, Department of Pediatric Surgery, Massachusetts General Hospital, Boston, Massachusetts
Ambiguous Genitalia

Agostino Pierro, MD, FRCS(Eng), FRCS(Ed), FAAP
Nuffield Professor of Paediatric Surgery and Head of Surgery Unit, Institute of Child Health, University College London; Consultant Paediatric Surgeon, Great Ormand Street Hospital for Children NHS Trust, London, United Kingdom
Neonatal Physiology and Metabolic Considerations

William P. Potsic, MD, MMM
Professor of Otorhinolaryngology–Head and Neck Surgery, University of Pennsylvania School of Medicine; Director, Division of Otolaryngology, and Vice Chair for Clinical Affairs, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania
Otolaryngologic Disorders

Pramod S. Puligandla, MD, MSc, FRCSC
Assistant Professor of Surgery and Pediatrics, McGill University Faculty of Medicine; Attending Staff, Division of Pediatric Surgery and Pediatric Critical Care Medicine, The Montreal Children's Hospital of the McGill University Health Center, Montreal, Quebec, Canada
Infections and Diseases of the Lungs, Pleura, and Medistinum

Devin P. Puapong, MD
Senior Surgical Resident, Kaiser Permanente Medical Center, Los Angeles,California
Duodenal Atresia and Stenosis—Annular Pancreas

Prem Puri, MS, FRCS, FRCS(Edin), FACS
Professor of Paediatrics, University College Dublin; Consultant Paediatric Surgeon and Director of Research, Children's Research Centre, Our Lady's Hospital for Sick Children, Crumlin, Dublin, Ireland
Intestinal Neuronal Dysplasia

Judson G. Randolph, MD
Professor of Surgery Emeritus, George Washington University School of Medicine and Health Sciences; Former Surgeon-in-Chief, Children's National Medical Center, Washington, DC
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Frederick J. Rescorla, MD
Professor of Surgery, Indiana University School of Medicine; Surgeon-in-Chief, Riley Hospital for Children, Indianapolis, Indiana
The Spleen

Jorge Reyes, MD
Professor of Surgery, University of Washington School of Medicine; Chief, Division of Transplant Surgery, University of Washington Medical Center, Seattle, Washington
Principles of Transplantation

Richard R. Ricketts, MD
Professor of Surgery, Emory University School of Medicine; Chief, Division of Pediatric Surgery, Children's Health Care of Atlanta at Egleston, Atlanta, Georgia
Mesenteric and Omental Cysts

Richard C. Rink, MD
Robert A. Garrett Professor of Pediatric Urologic Research and Professor of Urology, Indiana University School of Medicine; Chief, Pediatric Urology, Riley Hospital for Children, Indianapolis, Indiana
Incontinent and Continent Urinary Diversion

Risto J. Rintala, MD
Professor of Pediatric Surgery, University of Helsinki Medical Faculty; Chief, General Pediatric Surgery, Hospital for Children and Adolescents, Helsinki, Finland
Other Disorders of the Anus and Rectum, Anorectal Function

Albert P. Rocchini, MD
Professor of Pediatrics and Director of Pediatrics Cardiology, University of Michigan Redical School; Director of Pediatric Cardiology, University of Michigan Hospital, Ann Arbor
Neonatal Cardiovascular Physiology and Care

Heinz Rode, M Med(Chir), FCS(SA), FRCS(Edin)
Professor of Paediatric Surgery, University of Cape Town School of Child and Adolescent Health; Head of Pediatric Surgery, Red Cross Children's Hospital, Institute of Child Health, Cape Town, South Africa
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Bradley M. Rodgers, MD
Professor of Surgery and Pediatrics, University of Virginia School of Medicine; Chief, Division of Pediatric Surgery, Department of Surgery, University of Virginia Medical Center; Chief, Children's Surgery, UVA Children's Hospital, Charlottesville, Virginia
Laryngoscopy, Bronchoscopy, and Thoracoscopy

A. Michael Sadove MD, MS
James Harbaugh Professor of Surgery (Plastic), Indiana University School of Medicine; Chief of Plastic Surgery, Riley Hospital for Children, Indianapolis; Chairman of Surgery, Clarian North Medical Center, Carmel, Indiana
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Bob H. Saggi, MD
Assistant Professor of Surgery, Department of Surgery, Division of Immunology and Organ Transplantation, University of Texas Medical School at Houston; Staff Surgeon, Memorial Hermann Hospital, Houston, Texas
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Arthur P. Sanford, MD
Assistant Professor of Surgery, The University of Texas Medical Branch School of Medicine at Galveston; Staff Physician, Shriners Burns Hospital, Galveston, Texas
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L. R. Scherer III, MD
Associate Professor of Clinical Medicine, Indiana University School of Medicine; Director of Trauma, Riley Hospital for Children, Indianapolis, Indiana
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Jay J. Schnitzer, MD, PhD
Associate Professor of Surgery, Harvard Medical School; Associate Visiting Surgeon, Massachusetts General Hospital, Boston, Massachusetts
Ambiguous Genitalia

Marshall Z. Schwartz, MD
Professor of Surgery and Pediatrics, Drexel University College of Medicine; Director, Pediatric Surgery Research Laboratory, and Surgical Director, Pediatric Renal Transplantation, St. Christopher's Hospital for Children, Philadelphia, Pennsylvania
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Robert C. Shamberger, MD
Robert E. Gross Professor of Surgery, Harvard Medical School; Chief, Department of Surgery, Children's Hospital Boston, Boston, Massachusetts
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Nina L. Shapiro, MD
Associate Professor of Surgery/Pediatric Otolaryngology, David Geffen School of Medicine at UCLA; Attending Surgeon, UCLA Medical Center, Los Angeles, California
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Curtis A. Sheldon, MD
Professor, University of Cincinnati College of Medicine; Professor and Director (Pediatric Urology), Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio
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Stephen J. Shochat, MD
Professor of Surgery and Pediatrics, University of Tennessee School of Medicine; Surgeon-in-Chief and Chairman, Department of Surgery, St. Jude Children's Research Hospital, Memphis, Tennessee
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Michael A. Skinner, MD
Associate Professor of Surgery and Pediatric Surgery, Duke University School of Medicine, Durham, North Carolina
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C. D. Smith, MD, MS
Associate Professor of Surgery and Pediatrics, Medical University of South Carolina College of Medicine; Attending, Division of Pediatric Surgery, MUSC Medical Center, Charleston, South Carolina
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Jodi L. Smith, MD, PhD
Assistant Professor of Neurological Surgery, Department of Neurological Surgery, Indiana University School of Medicine; Pediatric Neurosurgeon, Riley Hospital for Children, Indianapolis, Indiana
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Samuel D. Smith, MD
Professor of Surgery, University of Arkansas for Medical Sciences College of Medicine; Chief of Pediatric Surgery, Arkansas Children's Hospital, Little Rock, Arkansas
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Charles L. Snyder, MD
Associate Professor of Surgery, University of Missouri–Kansas City School of Medicine, Kansas City, Missouri; Clinical Assistant Professor of Surgery, University of Kansas School of Medicine, Kansas City, Kansas; Director of Clinical Research, The Children's Mercy Hospital, Kansas City, Missouri
Meckel's Diverticulum

Lewis Spitz, MBChB, MD(Hon), PhD, FRCS, FRCPCH, FAAP(Hon), FCS(SA)(Hon)
Emeritus Nuffield Professor of Pediatric Surgery, Institute of Child Health, University College London; Consultant Paediatric Surgeon, Great Ormond Street Hospital, London, United Kingdom
Esophageal Replacement

Thomas L. Spray, MD
Professor of Surgery, University of Pennsylvania School of Medicine; Chief, Division of Cardiothoracic Surgery, and Alice Langdon Warner Endowed Chair in Pediatric Cardiothoracic Surgery, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania
Heart Transplantation

Thomas E. Starzl, MD, PhD
Distinguished Service Professor of Surgery, University of Pittsburgh School of Medicine; Director Emeritus, Thomas E. Starzl Transplantation Institute, Pittsburgh, Pennsylvania
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Charles J. H. Stolar, MD
Professor of Surgery and Pediatrics, Columbia University College of Physicians and Surgeons; Chief, Pediatric Surgery, Morgan Stanley Children's Hospital of New York–Presbyterian, New York, New York
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Phillip B. Storm, MD
Assistant Professor of Neurosurgery, University of Pennsylvania School of Medicine; Attending Neurosurgeon, Hospital of the University of Pennsylvania and The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania
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Steven Stylianos, MD
Professor of Surgery, University of Miami Leonard M. Miller School of Medicine; Chief, Department of Pediatric Surgery, Miami Children's Hospital, Miami, Florida
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Wendy T. Su, MD
Fellow, Pediatric Surgical Service, Memorial Sloan-Kettering Cancer Center, New York, New York
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Riccardo Superina, MD, CM, FRCSC, FACS
Professor of Surgery, Northwestern University, Director, Transplant Surgery, Children's Memoral Hospital, Chicago, Illinois
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David E. R. Sutherland, MD, PhD
Professor of Surgery, University of Minnesota Medical School; Head, Transplant Division, and Director, Diabetes Institute for Immunology and Transplantation, University of Minnesota Medical Center, Fairview, Minneapolis, Minnesota
Pancreas and Islet Cell Transplantation

Leslie N. Sutton, MD
Professor of Neurosurgery, University of Pennsylvania School of Medicine; Chairman, Division of Pediatric Neurosurgery, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania
Brain Tumors

Edward P. Tagge, MD
Professor of Surgery and Pediatrics, Division of Pediatric Surgery, Medical University of South Carolina College of Medicine; Attending Surgeon, MUSC Children's Hospital, Charleston, South Carolina
Wilms' Tumor

Daniel H. Teitelbaum, MD
Professor of Surgery, University of Michigan Medical School; Pediatric Surgeon, C.S. Mott Children's Hospital, Ann Arbor, Michigan
Nutritional Support; Hirschsprung's Disease and Related Neuromuscular Disorders of the Intestine

Claire L. Templeman, MD
Assistant Professor of Clinical Gynecology and Surgery, Keck School of Medicine at USC; Pediatric Surgeon, Children's Hospital Los Angeles, Los Angeles, California
Ovarian Tumors

Gonca Topuzlu Tekant, MD
Associate Professor of Pediatric Surgery, Istanbul University School of Medicine; Pediatric Surgeon, Cerrahpasa Medical Faculty, Istanbul, Turkey
Gastroesophageal Reflux Disease

Joseph J. Tepas III, MD
Professor of Surgery and Pediatrics, University of Florida College of Medicine; Staff Physician, Shands Jacksonville, Jacksonville, Florida
Vascular Injuries

Patrick B. Thomas, MD
Pediatric Surgery Fellow, Texas Children's Hospital, Baylor College of Medicine, Houston, Texas
Wilms' Tumor

Dana Mara Thompson, MD, MS
Associate Professor of Otorhinolaryngology, Mayo Graduate School of Medicine; Attending, Otorhinolaryngology Department, Mayo Clinic, Rochester, Minnesota
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Juan A. Tovar, MD, PhD
Professor of Surgical Pediatrics, Department of Pediatrics, Universidad Autonoma de Madrid; Head, Department of Pediatric Surgery, Hospital Universitario LaPaz, Madrid, Spain
Disorders of Esophageal Function

Jeffrey S. Upperman, MD, MA
Assistant Professor of Surgery, Keck School of Medicine of USC; Attending Surgeon, Children's Hospital Los Angeles, Los Angeles, California
Sepsis and Related Considerations

Joseph P. Vacanti, MD
John Homans Professor of Surgery, Harvard Medical School; Chief, Pediatric Surgery, Massachusetts General Hospital, Boston, Massachusetts
The Impact of Tissue Engineering in Pediatric Surgery

Dennis W. Vane, MD, MS, MBA
Professor of Surgery, University of Vermont College of Medicine; Chair, Pediatric Surgery, and Vice-Chair, Clinical Affairs, Department of Surgery, Fletcher Allen Health Care, Burlington, Vermont
Child Abuse and Birth Injuries

Mirjana Vustar, MD
Assistant Professor of Anesthesiology and Pediatrics, Vanderbilt University School of Medicine; Director, Pediatric Anesthesia Education, Vanderbilt Children's Hospital, Nashville, Tennessee
Pediatric Anesthesia

Brad W. Warner, MD
Professor of Surgery and Pediatrics, University of Cincinnati College of Medicine; Attending Surgeon and Director of Surgical Research, Division of Pediatric General and Thoracic Surgery, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio
Short-Bowel Syndrome

Thomas R. Weber, MD
Professor of Surgery, Saint Louis University School of Medicine; Director, Pediatric Surgery, Cardinal Glennon Children's Hospital, St. Louis, Missouri
Esophageal Rupture and Perforation

David E. Wesson, MD
Professor of Surgery and Chief, Division of Pediatric Surgery, Baylor College of Medicine; Chief, Pediatric Surgery Service, Texas Children's Hospital, Houston, Texas
Thoracic Injuries

Karen W. West, MD
Professor of Surgery, Indiana University School of Medicine; Director of ECMO, Riley Hospital for Children, Indianapolis, Indiana
Primary Peritonitis

Ralph F. Wetmore, MD
Professor of Otorhinolaryngology–Head and Neck Surgery, University of Pennsylvania School of Medicine; Senior Surgeon, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania
Otolaryngologic Disorders

Eugene Wiener, MD
Professor, Department of Surgery (Pediatric), University of Pittsburgh School of Medicine; Executive Vice President and Chief Medical Officer, Children's Hospital of Pittsburgh, Pittsburgh, Pennsylvania
Testicular Tumors

Jay M. Wilson, MD
Associate Professor of Surgery, Harvard Medical School; Attending, Children's Hospital Boston, Boston, Massachusetts
Respiratory Physiology and Care

Russell K. Woo, MD
Instructor in Surgery, Department of Surgery, Stanford University School of Medicine; Staff Physician, Stanford Hospital and Clinic, Stanford, and Lucile Packard Children's Hospital at Stanford, Palo Alto, California
New and Emerging Surgical Technologies and the Process of Innovation

Hsi-Yang Wu, MD
Assistant Professor of Urology, University of Pittsburgh School of Medicine; Director of Pediatric Urology Research, Children's Hospital of Pittsburgh, Pittsburgh, Pennsylvania
Testicular Tumors

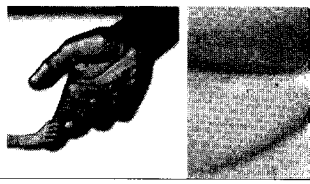
Elizabeth Yerkes, MD
Assistant Professor of Urology, Feinberg School of Medicine at Northwestern University; Attending Urologist, Children's Memorial Hospital, Chicago, Illinois
Incontinent and Continent Urinary Diversion

Daniel G. Young, MBChB, FRCS(Edin, Glasg), DTM&H
Honorary Senior Research Fellow, University of Glasgow; Former Head (Retired), Department of Surgical Pediatrics, Royal Hospital for Sick Children, Glasgow, United Kingdom
A Brief History of Pediatric Surgery

Moritz M. Ziegler, MD
Professor of Surgery, Division of Pediatric Surgery, University of Colorado School of Medicine; Surgeon-in-Chief, The Children's Hospital, Denver, Colorado
Meconium Ileus

The senior editors (from left to right): James A. O'Neill, Jr., Jay L. Grosfeld, Arnold G. Coran, and Eric W. Fonkalsrud.

Preface



The first edition of ***Pediatric Surgery*** was published by Year Book Medical Publishers in 1962, with Drs. Kenneth Welch, William Mustard, Mark Ravitch, Clifford Benson, and William Snyder serving as the initial Editorial Board. The project was conceived to meet the need for a comprehensive work on pediatric surgery, with the heaviest concentration focused in the traditional fields of general, thoracic, and urologic surgery. Numerous contributors participated in the development of this new textbook that would for the next 44 years be known worldwide as the leading comprehensive resource in the field of children's surgery. Four additional editions of the textbook have been published since that time.

It has been 8 years since the fifth edition of the book was published in 1998. In the interim, we have experienced a veritable explosion of new scientific information, characterized by the elucidation of the human genome, development of tissue engineering, and introduction of other new technologies that have clearly impacted methods of diagnosis and how we treat our patients.

The sixth edition has an international flair and contains 133 chapters prepared by contributors from the United States, Canada, Europe, Asia, Australia, New Zealand, and Africa. It was the intent of the editors to include expert contributors with a significant or unique experience in their respective areas of interest so that all of the chapters would comply with the goal of providing current and practical information that was very well referenced in a modern comprehensive and authoritative text. A significant number of new authors and coauthors participated in this effort. Among the new contributions is a chapter concerning the history of pediatric surgery, providing a brief background of the origins of our profession in the United Kingdom, United States, and Asia. Other new chapters include material on molecular clinical genetics and gene therapy, the impact of tissue engineering in pediatric surgery, new and emerging technologies in surgical science, principles of pediatric oncology/genetics and radiation therapy, small bowel transplantation, and adolescent bariatric surgery.

All the other chapters were significantly changed, updated, and often expanded with the addition of numerous recent references. Some examples include the current status of the fetus as a patient; congenital chest wall deformities, which now includes up-to-date information on the Nuss procedure; pediatric anesthesia; ethical and legal considerations; the genetics of Hirschsprung disease; new information on short bowel syndrome (i.e., the Step procedure); and the inclusion of minimally invasive surgical techniques (laparoscopy, thoracoscopy) embedded within each chapter where appropriate.

Other major revisions and updated material are included. In Part I: neonatal physiology and metabolic considerations, respiratory physiology and care, neonatal cardiovascular physiology and care, extracorporeal life support and cardiopulmonary failure, sepsis and related conditions, hematologic disorders, and nutrition; Part II: trauma (including burn care); Part III: major tumors of childhood; Part IV: organ transplantation (liver, lung, heart, pancreas, kidney, and surgical implications of bone marrow transplantation), which was also reorganized and updated with the new protocols and information regarding contemporary care techniques and outcomes; Part V: conditions affecting the head and neck; Part VI: thoracic conditions (including esophageal atresia and tracheoesophageal fistula, along with various other esophageal conditions, lung cysts, congenital diaphragmatic hernia, and others); Part VII: a very wide spectrum of common congenital and acquired abdominal conditions (including hernias, abdominal wall defects, intestinal atresia, meconium ileus, Hirschsprung's disease, anorectal malformations, duplications, inflammatory bowel disease, biliary atresia, choledochal cyst, pancreatic conditions, spleen, portal hypertension and others); Part VIII: genitourinary disorders; and Part IX: special areas of pediatric surgery (conjoined twins, congenital heart disease, hand and soft tissue, orthopedic, neurologic, and vascular disorders). Many of the chapters are well illustrated and enhanced with the use of charts, tables, radiographic images, photographs of gross pathology and histology, and operative techniques.

The Editorial Board for the sixth edition is composed of Drs. Jay L. Grosfeld, James A. O'Neill, Jr., Eric W. Fonkalsrud, and Arnold G. Coran. All four were members of the editorial group for the fifth edition. The initial editorial responsibility for chapter assignments was evenly distributed among the four senior editors. We are grateful to Dr. Anthony A. Caldamone, who ably served as the section editor for Part VIII, genitourinary disorders. Dr. Grosfeld served as chairman of the board and, as lead editor, was the final reviewer of the entire manuscript. We are indebted to the editors who preceded us in the prior five editions who set the standard that we have tried to uphold for the sixth edition of *Pediatric Surgery*.

The editors wish to thank our administrative assistants and secretaries Karen Jaeger, Donna Bock, Gale Fielding, Cheryl Peterson, and Carol Simmons, who in addition to their usual responsibilities, were willing to support us in

completing this effort. We recognize this would not have been accomplished without them and appreciate their many contributions. We also express our sincere appreciation and thanks to many contributors from around the world who have played an important role in the preparation of the sixth edition. We are grateful for their willingness to share their knowledge and expertise and for complying with the specified format of the textbook in a timely manner that allowed us to meet production deadlines.

We are also grateful to the Elsevier/Mosby publishing staff for their support and cooperation in maintaining a high standard in the development and preparation of the sixth edition. We wish to recognize Ms. Janice Gaillard, Senior Developmental Editor, and Faith Voit, Freelance Editor, who prepared the manuscript for production; Judith Fletcher, Publishing Director; and Ms. Linda Grigg, Senior Project Manager, who guided this book throughout the production process.

The photograph of the senior editors was taken in April 2005 during a meeting of the American Surgical Association. The editors have viewed their work in preparing the sixth edition of *Pediatric Surgery* as a labor of love, and we express our hope that the textbook will provide a valued special resource to practicing pediatric surgeons, those in training, and other professionals who care for infants and children. It is our hope that this textbook will serve as a resource that will benefit future generations of children affected with surgical illness thoughout the world.

THE EDITORS

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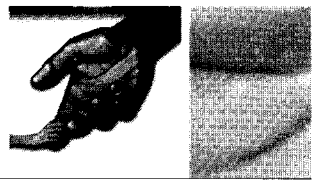

VOLUME ONE

VOLUME TWO

I

GENERAL

Chapter 1

A Brief History of Pediatric Surgery

Judson Randolph and Daniel G. Young

NORTH AMERICA

United States

The clinical practice of pediatric surgery had a rather haphazard start, but any recounting of the development of pediatric surgery in the United States must begin with William E. Ladd (Fig. 1-1). Born in 1880, Ladd graduated from Harvard College in 1903 and from Harvard Medical School in 1906. He also studied with several well-known Boston surgeons of the day. It was not until after World War I that Ladd, undoubtedly influenced by the Halifax disaster, began to spend increasing amounts of time ministering to the surgical needs of infants and children at Boston Children's Hospital. In 1927, at age 47, Ladd was named surgeon-in-chief at Children's Hospital.

The first practitioner of *pure* pediatric surgery in the United States was Dr. Herbert Coe of Seattle. He came east to observe the activities at Children's Hospital in Boston, where Ladd was occasionally present in the operating room. Coe went home to Seattle and in 1919 established the first exclusive practice of pediatric surgery in the United States (Ladd did not give up his adult work until 1927).

If Ladd can be considered the godfather of pediatric surgery in the United States, then his primary pupil, Dr. Robert E. Gross, was destined to become its guru. Born in 1905 and raised in Baltimore, Gross was the son of a piano maker. His father had young Bob work with a fellow craftsman in the hope that he would learn fine movements and detailed craftsmanship. In fact, he did. At Carlton College, Gross was headed for a career in chemistry. However, in his senior year, after reading Cushing's biography of Sir William Osler, he sought admission to Harvard Medical School and was accepted. He graduated in 1931 with an excellent record but did not obtain the surgical internship he coveted, so he entered the Harvard training program in pathology under Dr. S. Burt Wohlbach (Fig. 1-2). His subsequent work on surgical problems was highly influenced by his background in pathology.

In the combined training program in surgery at the Peter Bent Brigham Hospital and Children's Hospital,

Figure 1–1 The Ladd Medal, awarded by the Surgical Section of the American Academy of Pediatrics for achievement in pediatric surgery.

Figure 1–2 Robert E. Gross at his microscope during his residency in pathology at Harvard, 1932.

Figure 1–3 A group of North American surgeons attending a meeting of the British Association of Paediatric Surgeons, circa 1964. Front row (left to right): Mark Ravitch, Robert G. Allen, Harvey Beardmore (a Canadian), and Robert E. Gross. Back row (left to right): Lawrence K. Pickett, H. William Clatworthy, Hugh Lynn, Alexander Bill, C. Everett Koop, Willis Potts, Dan Cloud, and George Dorman.

Gross's genius began to emerge. He was always more of a mechanic than a physiologist. His observations in postmortem studies of children who had died of subacute bacterial endocarditis, originating in the patent ductus arteriosus, stimulated him to seek a surgical solution. First with pathologic specimens, then in the animal laboratory, Gross developed a carefully crafted technique for dividing the ductus. Finally in 1938 he selected as his first surgical candidate an 8-year-old girl who was dying from her patent ductus. Her recovery and subsequent course were highly gratifying.

When Gross performed this startling clinical triumph, he was 33 years old and an assistant resident in surgery at Brigham Hospital. This widely acclaimed event was a landmark in terms of addressing a clinical problem in the research laboratory and then bringing the solution to the operating room. After completing his surgical residency in 1939, Gross accepted Ladd's invitation to join him on the staff at Children's Hospital. Thereafter, Gross was instrumental in compiling Ladd's enormous experience in abdominal surgery in infants and children, and in 1941 they published a seminal textbook, *The Abdominal Surgery of Infants and Children.* In this remarkable text, the Ladd operation for malrotation of the intestine (initially described in 1936) and other unique approaches to the operative correction of anomalies in newborn infants were cataloged.

After Ladd's retirement, Gross was appointed surgeon-in-chief at Boston Children's Hospital. He also became the second incumbent of the William E. Ladd Chair in Children's Surgery, established under the aegis of Harvard Medical School in 1941.

Dr. Ovar Swenson, another surgeon at Children's Hospital, made some stellar contributions to pediatric surgery, particularly with regard to unraveling the dilemma of Hirschsprung's disease and defining its surgical solution. In 1950 he accepted the post of surgeon-in-chief at the Boston Floating Hospital, which was part of Tuft's Medical School.

During the 1940s, first under Ladd and then under Gross, a number of subsequently well-known pediatric surgeons received training at Children's Hospital (Fig. 1-3). Most notable were Dr. C. Everett Koop, who came to observe the surgical service for 7 months in 1946, and Dr. Willis Potts of Chicago, who also visited in 1946. After his stay in Boston, Koop returned to Philadelphia and began his long and prominent tenure as pediatric surgeon and professor at the University of Pennsylvania, based at the Children's Hospital of Philadelphia. Potts returned to Chicago and established an equally strong children's surgical program at Children's Memorial Hospital, which trained many outstanding pediatric surgeons.

Also in the circle of leading pediatric surgeons who benefited from their time at Boston Children's Hospital was Dr. H. William Clatworthy, the last resident trained by Ladd and the first trained by Gross. In 1950 Clatworthy began his distinguished career as surgeon in chief at the Columbus Children's Hospital at Ohio State University. Dr. Tague Chisholm left Boston in 1946 and joined Dr. Oswald Wyatt in Minneapolis. Dr. Alexander Bill also completed his training in Boston, including a significant role in the laboratory research that led to Swenson's operation for Hirschsprung's disease. He then joined Coe in 1947 at Children's Orthopedic Hospital in Seattle. Dr. Luther Longino, a taciturn surgeon from Arkansas, finished his residency under Gross in 1948 and stayed on as Gross's number-two departmental associate, where he remained for 20 years teaching legions of residents the technical aspects of surgery.

With vision and relentless energy, Coe badgered officials of the American Academy of Pediatrics until they created a Surgical Section in 1948.[17] Coe envisioned the newly created section as a national forum for pediatric surgeons to gather, exchange information, and gain recognition as a new force in American surgery.

By 1950, in addition to the structured program at Children's Hospital in Boston, one could acquire training in children's surgery as a preceptor, or as a 1- or

2-year fellow, at Chicago Memorial Children's Hospital under Potts, the Philadelphia Children's Hospital under Koop, the Boston Floating Hospital under Swenson, the Babies' Hospital in New York under a new program directed by Dr. Thomas Santulli, or the Children's Hospital of Los Angeles under Dr. William Snyder. In addition, there were well-established programs in Toronto and Montreal, Canada.[6] The output of many of these training programs was sporadic, and the graduates demonstrated a variety of experience—some with cardiac surgical training, some with urologic training, but all with broad experience in general pediatric surgery.

With the publication of his book, *The Surgery of Infancy and Childhood*, in 1953, Gross codified the specialty of pediatric surgery in North America. This masterful text described in meticulous detail Boston Children's Hospital's experience in general pediatric surgery, cardiac surgery, and urology.

In the United States and Canada the 1950s saw an increasing output of children's surgeons from a variety of training programs. Many of these graduates entered private practice. Concomitantly, and belatedly, there was a flurry of activity as children's hospitals sought trained pediatric surgeons to direct their surgical departments. Similarly, medical schools began to realize the necessity of adding to their faculties' surgeons who were specially trained in the surgical diseases of infants and children.

A watershed event in pediatric surgical education occurred in 1965. With great foresight, Clatworthy asked the Surgical Section of the American Academy of Pediatrics to form an Education Committee to evaluate the current educational processes of pediatric surgeons in the United States and Canada. Although the committee's primary mandate was the evaluation of existing training programs, it also made recommendations for basic principles and requirements for the education of pediatric surgeons. Originally, 11 programs in the United States and 2 in Canada were recommended by the committee as meeting the standards set forth in the Clatworthy report.

A number of important events coalesced to substantiate pediatric surgery as a bona fide surgical specialty in North America.[16] It occurred to Dr. Stephen Gans that the specialty required its own journal. With the aid of Koop as editor in chief, the *Journal of Pediatric Surgery* was born in 1966. In 1969 a chance meeting between Drs. Lucian Leape and Thomas Boles resulted in the concept of a new surgical society that would be unencumbered by any attachments to other associations, such as the American Academy of Pediatrics. The idea quickly took hold and, with a number of prominent founding members, the American Pediatric Surgical Association was launched in 1970, with Gross as its first president. Additional training programs, which had been carefully evaluated by the Clatworthy committee, were imposing a standard curriculum of pediatric surgical education.

Several requests that the American Board of Surgery establish a special board in pediatric surgery had been unsuccessful during the 1950s and 1960s. However, with the backing of a new independent surgical organization, inspected and standardized training programs, a journal devoted to the specialty, and insinuations into the curricula of general surgical training programs across the land,

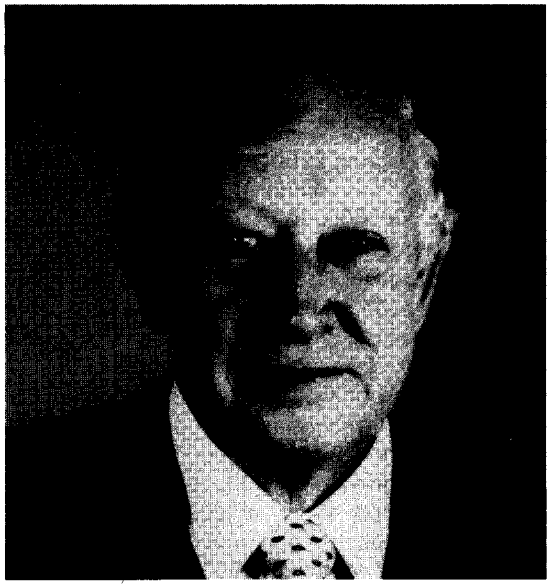

Figure 1–4 Harvey Beardmore, distinguished Canadian pediatric surgeon, fifth president of the American Pediatric Surgical Association, and leader in persuading the American Board of Surgery to grant a Certificate of Special Competence in Pediatric Surgery.

all that was lacking was a spokesperson to approach the American Board of Surgery again.[10] This role fell to Dr. Harvey Beardmore of Montreal (Fig. 1-4), a genial, diplomatic, highly intelligent, and persuasive individual. Beardmore, armed with the facts, succeeded where others had failed. The American Board of Surgery received the carefully prepared petition and in 1975 granted a new Certificate of Special Competence in Pediatric Surgery to be awarded to all qualified applicants.

Research undergirding the specialty of pediatric surgery first took the form of clinical advances in the 1930s and 1940s.[16] Ladd's operation for malrotation was a signal event. Gross's innovations involving the great vessels around the heart—the ductus, coarctation of the aorta, and vascular ring deformities—all deserve mention. Concomitantly, Blalock's triumph with the systemic-pulmonary shunt for babies with tetralogy of Fallot was another landmark. Potts's direct aortic–pulmonary artery shunt accomplished similar physiologic results but required a special clamp. When Potts and Smith developed such a clamp with many delicate teeth to hold a pulsatile vessel securely but gently, they implemented a technical advance that remains useful today in all aspects of vascular surgery. To bridge the gap in long, narrow coarctations, Gross devised the use of freeze-dried, radiated aortic allografts and demonstrated their long-term clinical function. This observation was the foundation for the development of all peripheral vascular surgery, making it a discovery worthy of international recognition. In addition, Swenson's meticulous studies of aganglionic megacolon, followed by his careful adaptation of Hochenegg's operation for removal of the rectum, has helped thousands of children with Hirschsprung's disease.

Research in biology affecting adult surgical patients also began to be commingled with research specifically adapted to children. Studies of body composition as

defined by Francis D. Moore were adapted to infants by Rowe, Moore, Artz, Moncrief, and Pruitt added to our knowledge of burn care, which was then used by one of their primary pupils, James O'Neill, to treat burned children. Stanley Dudrick, pioneer with Drs. Rhoads and Wilmore in the use of intravenous nutrition to sustain surgical patients, has created the science of surgical nutrition, saving countless patients of all ages. Bartlett instituted extended extracorporeal oxygenation for infants with temporary inadequate lung function; this technique has now been expanded into important lifesaving techniques for older children and adults. Exquisitely precise care of trauma patients from beginning to end, originally espoused by Cowley and now adapted in child care by Haller, Eichelberger, O'Neill, Tepas, and many others, has allowed the survival of many children who would otherwise have been lost to the ravages of injury.

The awe-inspiring field of transplantation led by Murray, Starzl, Shumway, and many others continues to open new avenues of treatment in an ever-expanding number of diseases in patients of all ages. Jackson of Richmond, followed by DeLorimier in San Francisco, began experimenting with fetal surgery. DeLorimier's prize student, Harrison, and his disciples are now pursuing clinical investigations into the practicalities of this new form of surgical therapy.

Fundamental fetal research is under way in the laboratories of Dr. Patricia Donohoe as she investigates the growth factors influencing embryologic development. Her work has led to the defining of müllerian inhibitory substance, which influences sexual development. Among the many interlinking studies of malignant diseases affecting adults and children, none is more important or has more potential than the work of Judah Folkman of Boston Children's Hospital. Folkman discovered the angiogenesis of malignant tumors, which led him to postulate and search for methods of using antiangiogenesis as a cancer inhibitor. Thus, a whole new science has been created in the field of oncology.

Today, major advances in clinical pediatric surgery, education, and research continue to unfold based on the achievements of the past, and many of these contributions are extending to adult surgery as well.

Canada

As events in children's surgery were unfolding in the United States, Canadian pediatric surgery was experiencing a parallel evolution, primarily at three major institutions. Dr. Alexander Forbes, an orthopedic surgeon, played a key role at the Montreal Children's Hospital from 1904 to 1929. Dr. Dudley Ross, who led the Department of Surgery at Montreal Children's Hospital from 1937 to 1954, was largely responsible for establishing a modern children's surgical unit in the province of Quebec. In 1948 Ross reported the first successful rescue in Canada of a baby with esophageal atresia.[4] Following Ross, Dr. David Murphy served as chief of pediatric surgery and director of the emerging pediatric surgical training program from 1954 to 1974. He was ably assisted by Dr. Herbert Owen, Dr. Gordon Karn, and his first trainee (1954), Dr. Harvey Beardmore, who went on to establish an international reputation. Beardmore served as chief of surgery at Montreal Children's Hospital during the 1970s and was followed by Dr. Frank Guttman from 1981 to 1994.

In Toronto, the Hospital for Sick Children was established in 1875 by Mrs. Samuel McMaster (whose husband founded McMaster University).[5] As in the United States, surgeons who treated adults answered the call for pediatric surgery at the end of the 19th and beginning of the 20th centuries. Perhaps the most distinguished Toronto surgeon was Dr. W. Edward Gallie, who served as chief surgeon at the Hospital for Sick Children from 1921 to 1929. Gallie was named to the chair in surgery at the University of Toronto, where he established the Gallie surgical training program. In Canada the Gallie School of Surgery became the equivalent of that at Johns Hopkins, led by Dr. William Halsted. With the expansion of Gallie's responsibilities, he relinquished his role as chief of pediatric surgery to Dr. Donald Robertson, an adventuresome thoracic surgeon who held the post until 1944, retiring almost concomitantly with Ladd in Boston. Dr. Arthur Lemesurer, an inventive plastic surgeon, began a general pediatric surgical training program that produced, beginning in 1949, Clinton Stephens, James Simpson, Robert Salter, Phillip Ashmore, Donald Marshall, and Stanley Mercer, to name the most illustrious graduates, all of whom would become leaders in the field of pediatric surgery throughout Canada.

In 1956 Dr. Alfred Farmer was chosen surgeon-in-chief at Toronto's Hospital for Sick Children and immediately formed several specialty surgical divisions, including one for general pediatric surgery. It was a landmark stroke, according to Dr. Clinton Stephens, which allowed separate specialty leadership under the wise direction of Dr. Stewart Thomson from 1956 to 1966 and Stephens himself from 1966 to 1976 (S. Ein, personal communication). During these 2 decades there was a prodigious output in clinical work and clinical research and an impressive roster of graduating trainees. The tradition of excellence in all aspects of pediatric surgery was expanded with the appointment in 1977 of Dr. Robert Filler.

A third children's hospital, the Hospital Sainte-Justine in Montreal, has also contributed richly to children's surgery. Founded in 1907 by Mrs. Justine Lacoste-Beau-Bien, the hospital was combined with the Francophone Obstetrical Unit of Montreal, creating one of the largest maternal and child care centers in North America. Dr. Pierre-Paul Collin came to the hospital in 1954, bringing thoracic surgical experience and a commitment to child care. He trained a number of Canada's latter-day leaders in pediatric surgery, including Frank Guttman, Herve Blanchard, Saleem Yazbeck, and Jean-Martin LaBerge.

From these three key surgical centers, leadership and progress spread across the provinces with the same comprehensive effect seen in the United States.

UNITED KINGDOM

Jean-Jacques Rousseau, the Swiss-French philosopher and moralist, commented in the mid-18th century, "One half of the children born die before their eighth year.

That is Nature's law; why try to contradict it?" This attitude pervaded 18th-century thought. The development of pediatric surgery did not occur until much later, despite the observation that "surgeons and apothecaries are oftener called to cure children than many physicians of greater eminence."

Pediatrics began to occupy the thoughts of doctors and the general population with the development of many foundling hospitals in Britain and elsewhere in Europe. The best known of these in Britain still exists as the Coram Foundation.[13] It was originally established in Holborn, London (1739), close to the current location of the Hospital for Sick Children on Great Ormond Street. Like many other institutions of its kind, although it was called a hospital, it was more of a care home than a treatment center. Hospitals for children, as we understand them today, evolved in the 19th century.

In Europe the major landmark in the development of children's hospitals, and in the evolution of pediatric surgery, was the establishment of the Hôpital des Enfants Malades in Paris in 1802. This 200-bed unit provided treatment for children with medical or surgical disorders. Children younger than 7 years were not allowed admission to other hospitals in Paris. Subsequently, there was a steady movement toward establishing children's hospitals in the main cities in Europe.

In 1852 the Hospital for Sick Children (HSC) opened its doors in a converted house on Great Ormond Street.[7] This hospital was the brainchild of Dr. Charles West, aided by Dr. Bence Jones. West's philosophy was that children with diseases of a medical nature required special facilities and attention, but that those with surgical disorders (at the time, mostly trauma related) could be treated in general hospitals. This attitude took a long time to die from the minds of some pediatricians and is still in evidence in some parts of the world.

West opposed the appointment of a surgeon to the staff of the HSC, but the board disagreed and appointed G. D. Pollock. Pollock soon resigned and was replaced in 1853 by Athol Johnson. Johnson's insight into the scope of surgery for children was presented in three long papers published in the *British Medical Journal* in 1861.[9] T. Holmes, who followed Johnson, published his 37-chapter book, *Surgical Treatment of the Diseases of Infancy and Childhood*, in 1868.[8] Although the specialty of pediatrics, let alone pediatric surgery, had not yet developed, it is clear that surgery for children was already a special field.

Pediatrics in the 19th century was split. One approach was the pattern established in Paris, whereby children were treated in hospitals specially oriented toward children's care. The alternative was the West approach, common in Britain in the second half of the 19th century.[11] There, a number of children's hospitals, such as those in Birmingham and Edinburgh, were established to provide medical treatment but not surgery for children. Around the same time, Charles Dickens,[12] a vital supporter of the HSC, clearly believed in the importance of special facilities for all children who needed hospitalization. Some centers recognized the special requirements of children with surgical disorders. For example, at the Royal Hospital for Sick Children in Glasgow (RHSC), established after a 21-year gestation period, the board appointed equal numbers of medical specialists and surgical specialists.[19] Laypeople appear to have understood the importance of both medical and surgical services for children.

The latter part of the 19th century saw a major expansion in surgery for children owing to the development of ether and chloroform anesthesia in midcentury and the gradual acceptance of antiseptic surgery. Although carbolic acid had been used earlier, English surgeon Joseph Lister gave the main impetus to the concept of antiseptic surgery. After qualifying in London, he developed his antiseptic approach in Glasgow before moving to Edinburgh and then to King's College, London. One of Lister's young assistants in Glasgow was William Macewen (later Sir William), known as the father of neurosurgery and one of the original surgeons appointed to the RHSC.

In Scotland, where pediatric care was generally ahead of the rest of Britain, the Royal Edinburgh Hospital for Sick Children (REHSC) opened in 1860. It was not until 1887, however, that the board decided to set aside a ward for surgical patients and to use the sewing room as an operating theater.[14] Joseph Bell (president of the Royal College of Surgeons of Edinburgh), Sir Harold Styles (who performed pyloromyotomy the year before Conrad Ramstedt), Sir John Fraser (author of a widely used two-volume textbook, *Surgery of Childhood*), and James J. Mason Brown (also a president of the Royal College of Surgeons of Edinburgh and author of a book titled *Surgery of Childhood*) were the senior surgeons from 1887 to 1964. It is of interest that Gertrude Hertzfeld held a surgical appointment at the REHSC from 1919 to 1947—one of the few women surgeons of that era.

Back in the 19th century, training in pediatric surgery, independent of general surgery, was given in Glasgow. The syllabus of lectures at St. Mungo College in Glasgow is extensive, and an example from 1889-1890 is shown in Table 1-1. A similar 15-lecture course was given on medical diseases.

Soon after these hospitals opened, their boards recognized the need for the development of dispensaries or outpatient departments. In Manchester, the dispensary actually preceded the hospital at Pendelbury. These dispensaries handled many surgical patients, and much of what is called pediatric surgery was done there. One of the most outstanding surgeons of that generation was James Nicoll, who reported 10 years of his work in 1909,[15] one of more than 100 of his publications. He is now known as the Father of Day Surgery, but the title of pediatric surgeon was equally merited, although only part of his time was devoted to children's surgery (Table 1-2). He performed pyloromyotomy with success in the late 19th century in a somewhat different fashion from Styles and Ramstedt.

Although invited to take charge of one of the two surgical units in 1914, Nicoll rejected the offer because he would have been required to give up his adult practice. He preferred the less prestigious position of dispensary surgeon to that of visiting surgeon. The board of the RHSC had decided that physicians or surgeons appointed to the hospital had to devote all their professional time to the treatment of children; the board might grant an exception for some specific work, but it had to

TABLE 1-1 St. Mungo College Syllabus: 1889-1890

Surgical Diseases of Children

Lecturer: James A. Adams, MD, FFPSG, Assistant Surgeon to the Royal Infirmary

The course will be delivered during the summer session at 11:30 am, on Tuesdays and Thursdays, and will include a consideration of the following subjects:

1. The management of infants and children during illness
2. Diathesis—hemorrhagic, tuberculosis, struma, rachitis, etc.
3. Syphilis
4. Fractures
5. Dislocations
6. Affections of the joints
7. Diseases of periosteum and bone
8. Glandular disease—cervical, axillary, femoral, Hodgkin's disease
9. Congenital malformations—harelip, cleft palate, spina bifida and encephalocele, talipes, wry neck, imperforate anus and rectum, malformations of foot and hand
10. Tumors—innocent, malignant, congenital
11. Diphtheria—laryngitis, croup, tracheotomy and its alternatives
12. Burns—scalds, subsequent deformities
13. Diseases of the spinal column—caries, angular and lateral curvature
14. Empyema—hydrothorax
15. Paralysis—pseudohypertrophic, tetany, spastic paralysis, neuroninesis, etc.
16. Genitourinary affections—extroversion of the bladder, hypospadias, phimosis, paraphimosis, masturbation, hermaphroditism, calculus, lithotomy, lithotrity, incontinence of urine
17. Hernia
18. Abdominal diseases—peritonitis, obstruction, tabes, tumors, rectum and anus
19. Organs of special sense
20. Aural disease—its influence on intracranial abscess
21. Foreign bodies in eye, ear, nose, etc.

TABLE 1-2 Types of Outpatient Operations Performed by James Nicholl, Royal Hospital for Sick Children, Glasgow: 1899-1908*

Tuberculosis
Talipes
Harelip and cleft palate
Mastoid empyema
Spina bifida
Fracture
Pyloric stenosis

*In this 10-year period, 7392 of 8988 operations were done by Nicholl.

be secondary to the surgeon's duties at the children's hospital. Clearly, an outside practice was undesirable.

Alex MacLennan was first appointed a dispensary surgeon at the RHSC in 1902, then a visiting surgeon in 1914. In 1919 the University of Glasgow was given money to establish both a medical and a surgical lectureship, the first academic appointments in the specialty in Britain. MacLennan was appointed Barclay lecturer in surgical and orthopedic diseases of children at the University of Glasgow in 1919 and continued in this post until he retired in 1938. His particular interest was in orthopedics; his successor, Matthew White, appointed to the dispensary in 1924, visiting surgeon in 1930, and Barclay lecturer in 1938, was a thoracic and abdominal surgeon. Wallace Dennison and Dan Young were among the other surgeons who later filled these posts.

Meantime, in Edinburgh, the children's surgical services and the adult services remained closely associated until Mason Brown became the chief. Contrary to the statement that "Scotland had paediatric surgeons for a long time, but they practiced only children's surgery until an adult job became vacant,"[18] surgeons at the children's hospitals in both Edinburgh and Glasgow refused to accept prestigious posts in adult surgery because they were dedicated to their children's work. The archives of these institutions record these facts.

To many, pediatric surgery was a development that took place shortly after the Second World War. Contributing to that development were other factors, such as the introduction of the National Health Service in Britain, providing "free" treatment for all individuals irrespective of age or social circumstance. Developments unrelated to medicine, such as the plastics industry and many other technical innovations in the mid-20th century, allowed great strides, particularly in neonatal surgery. A closer look, however, shows that pediatric surgery had been developing over many decades, although the first surgical pediatric "clubs"—the Scottish Surgical Paediatric Club and the Surgical Section of the American Academy of Pediatrics—were established in 1948.[1,2,17]

Developments in the specialty were closely related to committed individuals. Denis Browne, an Australian initially appointed to the HSC in London in 1924, spent his professional life committed to pediatric surgery. In London and elsewhere in England, general surgeons who were interested in pediatric surgery carried on their pediatric practices in the cities, along with their adult practices. Financial considerations were no doubt important, because few were able to sustain themselves on a pediatric surgical practice alone, irrespective of their desire. Browne was the first surgeon in London to confine himself to pediatric surgery. He developed a large number of admirers and disciples over the years. He was widely known, and his tall stature made him easily recognizable. All who knew him would agree that he had a somewhat dominating and domineering manner and did not easily accept contradiction of his views or theories. Browne's longtime colleague James Crooks called him an "intellectual adventurer, a rebel and a cynic." Even a few days before his death, Browne was "still the supreme egotist."[3] His faithful secretary recounts that when she attempted to get Browne to tone down some of his letters, a friend told her, "You must be crazy! It has taken DB all his life to build this reputation for rudeness and you come along at the eleventh hour to wreck it."[20]

Figure 1–5 Denis Browne Gold Medal. *A*, Front of the medal. *B*, Back of the medal, which reads, "The aim of paediatric surgery is to set a standard not to seek a monopoly."

One of us (Young) worked as his last assistant in his private work and found him stimulating and straightforward. The Denis Browne Gold Medal remains a memento of his presence and clearly demonstrates his views (Fig. 1-5).

After the Second World War, many surgeons from overseas spent some time in the United Kingdom; the majority visited the HSC, where they came under the influence of Browne and some of the other surgeons mentioned. Many subsequently established internationally recognized centers on many continents. Jannie Louw, Douglas Stephens, Durham Smith, and Christian Barnard are a few examples.

Browne's major interest was in the structural anomalies, and he achieved widespread recognition for his advocacy of intrauterine pressure contributing to or causing such anomalies. He had as contemporaries and senior colleagues at the HSC such men as L. Barrington-Ward and T. Twistington Higgins, surgeons of considerable stature, so it was in his latter days that he emerged as the dominant surgeon at Grand Ormond Street. It was Higgins who initially held discussions in London that led to the formation of the British Association of Paediatric Surgeons; Browne was then the senior surgeon at the HSC and became the association's first and longest-serving president. In his latter years in the National Health Service, his colleagues included George McNab (introducer of the Holter valve for hydrocephalus), David Waterston (early pediatric cardiac surgeon), and Sir David Innes Williams (doyen pediatric urologist of Britain). Each of these outstanding men made contributions to the development of pediatric surgery.

Many other developments were also taking place. Andrew Wilkinson and others such as Ole Knutrud from Oslo were studying infant metabolism. Isabella Forshall (later joined by Rickham) was a caring surgeon who established an excellent clinical service, although she made no major scientific contributions. Her 1959 Christmas card pictured a number of prominent individuals at the British Association of Paediatric Surgeons' meeting (Fig. 1-6).

In summary, the history of pediatric surgery on the east side of the Atlantic reveals a division in approach through much of the 19th and 20th centuries. In recent decades, there has been less divergence, but each society has come up with its own solutions to the steadily improving care of infants and children requiring surgery. The past 50 years have seen many changes, and the more recent details are covered in individual chapters.

ASIA

Space constraints prevent a full recounting of the development of pediatric surgery in Asia.* However, it must be acknowledged that the worldwide literature is replete with contributions from Japan, China, Taiwan, and other Asian sources. Zhang in China survived the Cultural Revolution to emerge as that nation's father figure in children's surgery, and there is now a new generation of surgeons.

Pediatric surgery in Japan did not develop until some years after World War II. The first generation of pediatric surgeons appeared in the early 1950s: Ueda in Osaka, Suruga at Juntendo University in Tokyo, Kasai in Sendai, and Ikeda in Fukuoka. Suruga performed the first operation for intestinal atresia in 1952, and Kasai performed the first hepatoportoenterostomy for biliary atresia in 1955. The first children's hospital was the National Children's Hospital in Tokyo, established in 1965. The first Department of Pediatric Surgery was established at Juntendo University in Tokyo in 1968 by Suruga; today, training programs exist in nearly all the major university centers. The Japanese Society of Pediatric Surgeons and its journal were established in 1964, paralleling developments in other parts of the world. The second generation of pediatric surgeons includes Okamoto and

*The information in this section was provided by Professor Takeshi Miyano, Juntendo University, Tokyo, Japan.

Figure 1–6 Isabella Forshall's 1959 Christmas card. Seated (left to right): D. Waterston, M. Grob, I. Forshall, C. Koop, and D. Browne. Standing: H. Beardmore, R. Zachary, I. Kirkland, T. Ehrenpries, W. Dennison, H. Johnson, A. Wilkinsoon, A. Jolleys, J. Bentley, B. Smyth, V. Swain, H. Nixon, and B. O'Donnell. Missing from the photo is G. McNab.

Okada in Osaka; Akiyama, Tsuchida, and Miyano in Tokyo; Ohi in Sendai; and Suita in Fukuoka. All these individuals have made seminal contributions in the fields of nutrition, biliary and pancreatic disease, oncology, and intestinal disorders.

In recent decades, laboratories and clinical centers in Asia, particularly in Japan, have generated exciting new information in the clinical and basic biologic sciences that continues to enrich the field of children's surgery. Pediatric surgery has truly become internationalized in terms of clinical developments, education, and research, and the future looks promising.

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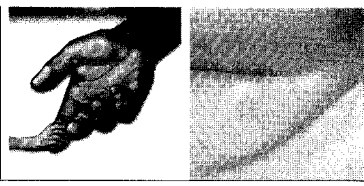
Chapter 2



Molecular Clinical Genetics and Gene Therapy

Alan W. Flake

The topics of this chapter are broad in scope and outside the realm of a classic core education in pediatric surgery. However, both molecular genetics and gene therapy will be of increasing clinical importance in all medical specialties, including pediatric surgery, in the near future. A few conservative predictions include improvements in the diagnostic accuracy and prediction of phenotype, the development of new therapeutic options for many disorders, and the optimization of pharmacotherapy based on patient genotype, but there are many other possible uses. The goal here is to provide an overview of recent developments that are relevant or potentially relevant to pediatric surgery.

MOLECULAR CLINICAL GENETICS

Although hereditary disease has been recognized for centuries, only relatively recently has heredity become the prevailing explanation for numerous human diseases. Before the 1970s, physicians considered genetic diseases to be relatively rare and irrelevant to clinical care. With the advent of rapid advances in molecular genetics, we currently recognize that genes are critical factors in virtually all human diseases. Although an incomplete indicator, McKusick's *Mendelian Inheritance in Man* has grown from about 1500 entries in 1965 to 10,000 in 2000, documenting the acceleration of knowledge in human genetics.[44] Even disorders that were once considered to be purely acquired, such as infectious diseases, are now recognized to be influenced by genetic mechanisms of inherent vulnerability and genetically driven immune system responses.

Despite this phenomenal increase in genetic information and the associated insight into human disease, there remains a wide gap between the identification of genotypic abnormalities that are linked to phenotypic manifestations in humans and any practical application to patient treatment. With the notable exceptions of genetic counseling and prenatal diagnosis, molecular genetics presently has little impact on the daily practice of medicine or, more specifically, on the practice of pediatric surgery. The promise of molecular genetics cannot be denied, however. Identifying the fundamental basis of human disorders and of individual responses to environmental, pharmacologic, and disease-induced perturbations is the first step toward understanding the downstream pathways that may have a profound impact on clinical therapy. The ultimate application of genetics would be the correction of germline defects for affected individuals and their progeny. Although germline correction remains a future fantasy fraught with ethical controversy,[56] there is no question that molecular genetics will begin to impact clinical practice in myriad ways within the next decade. A comprehensive discussion of the field of molecular genetics is beyond the scope of this chapter, and there are many sources of information on the clinical genetics of pediatric surgical disorders.

Human Molecular Genetics and Pediatric Surgical Disease

The rapid identification of genes associated with human disease has revolutionized the field of medical genetics, providing more accurate diagnostic, prognostic, and potentially therapeutic tools. However, increased knowledge is always associated with increased complexity. Whereas the classic model assumed that the spread of certain traits in families is associated with the transmission of a single molecular defect—with individual alleles segregating into families according to Mendel's laws—today's model recognizes that very few phenotypes can be satisfactorily explained by a mutation at a single gene locus. The phenotypic diversity recognized in disorders that were once considered monogenic has led to a reconceptualization of genetic disease. Although mendelian models are useful for identifying the primary cause of familial disorders, they appear to be incomplete as models of the true physiologic and cellular nature of defects.[15,66,71] Numerous disorders that were initially

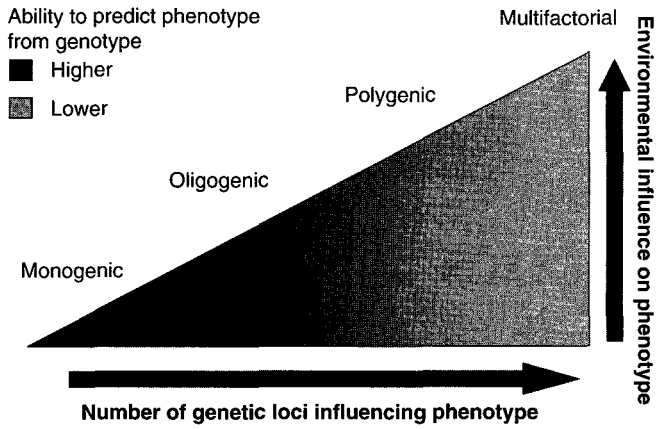


Figure 2-1 Conceptual continuum of modern molecular genetics. The genetic characterization of a disorder depends on (1) whether a major locus makes a dominant contribution to the phenotype, (2) the number of loci that influence the phenotype, and (3) the presence and extent of environmental influence on phenotype. The farther toward the right a disorder lies, the greater the complexity of the genetic analysis and the less predictive genotype is of phenotype.

characterized as monogenic are proving to be either caused or modulated by the action of a small number of loci. These disorders are described as oligogenic disorders, an evolving concept that encompasses a large spectrum of phenotypes that are neither monogenic nor polygenic. In contrast to polygenic or complex traits—which are thought to result from poorly understood interactions between many genes and the environment—oligogenic disorders are primarily genetic in etiology but require the synergistic action of mutant alleles at a small number of loci. One can look at modern molecular genetics as a conceptual continuum between classic mendelian and complex traits (Fig. 2-1). The position of any given disorder along this continuum depends on three main variables: (1) whether a major locus makes a dominant contribution to the phenotype, (2) the number of loci that influence the phenotype, and (3) the presence and extent of environmental influence on phenotype.

Disease-Specific Examples of Changing Concepts in Molecular Genetics

Monogenic Disorders

Cystic fibrosis (CF) is an example of a disorder close to the monogenic end of the continuum, but it also illustrates the complexity of the genetics of some disorders, even when a mutation of a major locus is the primary determinant of phenotype. On the basis of the observed autosomal recessive inheritance in families, the gene *CFTR* (cystic fibrosis transmembrane conductance regulator) was first mapped in humans to chromosome 7q31.2.[68] Once the *CFTR* gene was cloned,[62] it was widely anticipated that mutation analyses might be sufficient to predict the clinical outcome of patients. However, analyses of *CFTR* mutations in large and ethnically diverse cohorts indicated that this assumption was an oversimplification of the true genetic nature of this phenotype, particularly with respect to the substantial phenotypic variability observed in some CF patients. For instance, although *CFTR* mutations show a degree of correlation with the severity of pancreatic disease, the severity of the pulmonary phenotype—which is the main cause of mortality—is difficult to predict.[1,16,45] Realization of the limitations of a pure monogenic model prompted an evaluation of more complex inheritance schemes. This led to the mapping of a modifier locus for the intestinal component of CF in both human and mouse.[63,73] Further phenotypic analysis led to the discovery of several other loci linked to phenotype, including (1) the association of low-expressing mannose-binding lectin (*MBL;* also known as *MBL2*) alleles, human leukocyte antigen (*HLA*) class II polymorphisms, and variants in tumor necrosis factor-α (*TNFα*) and transforming growth factor-β-1 (*TGFβ1*) with pulmonary aspects of the disease[5,6,21,30]; (2) the correlation of intronic nitric oxide synthase 1 (*NOS1*) polymorphisms with variability in the frequency and severity of microbial infections[22]; and (3) the contribution of mucin 1 (*Muc1*) to the gastrointestinal aspects of the CF phenotype in mice (Fig. 2-2).[55] Recently, further layers of complexity have been discovered for both *CFTR* and its associated phenotype. First, heterozygous CF mutations have been associated with susceptibility to rhinosinusitis, an established polygenic trait.[69] Second, and perhaps more surprising, a recent study reported that some patients with a milder CF phenotype do not have any mutations in *CFTR*. This indicates that the hypothesis that *CFTR* gene dysfunction is requisite for the development of CF might not be true.[23]

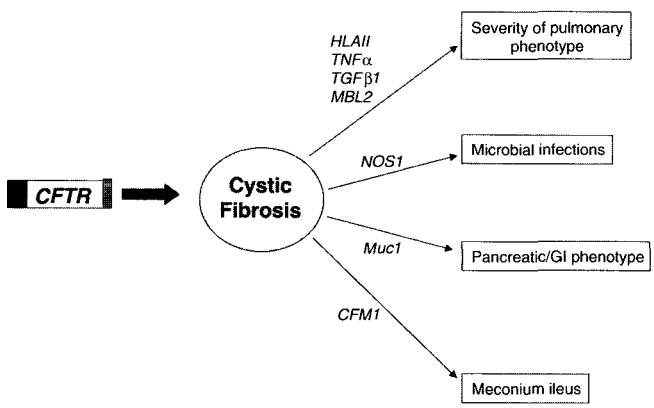


Figure 2-2 Complexity in monogenic diseases. Mutations in the cystic fibrosis transmembrane conductance regulator *(CFTR)* almost always cause the cystic fibrosis (CF) phenotype. Owing to modification effects by other genetic factors, the presence and nature of mutations at the *CFTR* locus cannot predict the phenotypic manifestation of the disease. Therefore, although CF is considered a mendelian recessive disease, the phenotype in each patient depends on a discrete number of alleles at different loci. *CFM1,* cystic fibrosis modifier 1; GI, gastrointestinal; HLAII, major histocompatibility complex class II antigen; *MBL2,* mannose-binding lectin (protein C) 2; *Muc1,* mucin 1; *NOS1,* nitric oxide synthase 1; *TGFβ1,* transforming growth factor-β-1; *TNF* α, tumor necrosis factor-α encoding gene.

Oligogenic Disorders

Recent developments in defining the molecular genetics of Hirschsprung's disease (HD) exemplify a relatively new concept in genetics—the oligogenic disorder. Although mathematical analyses of oligogenicity are beyond the scope of this discussion,[18,47] it is important to recognize that modifications of traditional linkage approaches are useful tools for the study of oligogenic diseases, especially if a major locus that contributes greatly to the phenotype is known. In the case of HD, two main phenotypic groups can be distinguished on the basis of the extent of aganglionosis: short-segment HD (S-HD) and the more severe long-segment HD (L-HD). Autosomal dominant inheritance with incomplete penetrance has been proposed for L-HD, whereas complex inheritance that involves an autosomal recessive trait has been observed in S-HD. Oligogenicity has been established in both HD variants by virtue of several factors: a recurrence risk that varies from 3% to 25%, depending on the length of aganglionosis and the sex of the patient; heritability values close to 100%, which indicates an exclusively genetic basis; significant clinical variability and reduced penetrance; and nonrandom association of hypomorphic changes in the endothelin receptor type B *(EDNRB),* with rearranged during transfection *(RET)* polymorphisms and HD.[54,57] So far, a combination of linkage, positional cloning studies, and functional candidate gene analyses has identified eight HD genes (Table 2-1),[2] of which the proto-oncogene *RET* is thought to be the main predisposing locus,[4,39] particularly in families with a high incidence of L-HD.[20]

The nonmendelian transmission of HD has hindered the identification of predisposing modifier loci by conventional linkage approaches. When these approaches (parametric and nonparametric linkage studies) were carried out on a group of 12 L-HD families, very weak linkage was observed on 9q31. However, based on the hypothesis that only milder *RET* mutations could be associated with another locus, families were categorized according to the *RET* mutational data. Significant linkage on 9q31 was detected when families with potentially weak *RET* mutations were analyzed independently,[39] indicating that mild *RET* alleles, in conjunction with alleles at an unknown gene on chromosome 9, might be required for pathogenesis. The mode of inheritance in S-HD has proved to be more complex than in L-HD, requiring further adjustments to the linkage strategies. Recently, the application of model-free linkage, without assumptions about the number and inheritance mode of segregating factors, showed that a three-locus segregation was both necessary and sufficient to manifest S-HD, with *RET* being the main locus, and that the transmission of susceptibility alleles was additive.[20]

The inheritance patterns observed in disorders such as HD illustrate the power of both expanded models of disease inheritance that account for reduced penetrance and phenotypic variability and the ability of these models to genetically map loci involved in oligogenic diseases—a first step toward identifying their underlying genes. More important, the establishment of nonmendelian models caused a change of perception in human genetics, which in turn accelerated the discovery of oligogenic traits.

Polygenic or Complex Disorders

Polygenic or complex disorders are thought to result from poorly understood interactions between many genes and the environment. An example of a polygenic

TABLE 2-1 Genes Associated with Hirschsprung's Disease and Relationship to Associated Anomalies

Gene	Gene Locus	Gene Product	Inheritance	Population Frequency (%)	Associated Anomalies	Incidence in HD (%)
RET	10q11.2	Coreceptor for GDNF	AD	17-38 (S-HD) 70-80 (L-HD) 50 (familial) 15-35 (sporadic)	CCHS MEN2A MEN2B	1.8-1.9 2.5-5.0 Unknown
GDNF	5p12-13.1	Ligand for RET and GFRα-1	AD	<1*	CCHS	1.8-1.9
NTN	19p13.3	Ligand for RET and GFRα-2	AD	<1*	Unknown	—
GFRα-1	10q26	Coreceptor for GDNF	Unknown	†	Unknown	—
EDNRB	13q22	Receptor for EDN3	AD/AR	3-7	Waardenburg's syndrome	Unknown
EDN3	20q13.2-13.3	Ligand for EDNRB	AD/AR	5	CCHS Waardenburg's syndrome	1.8-1.9 Unknown
ECE-1	1p36.1	EDN3 processing gene	AD	<1	Unknown	—
SOX10	22q13.1	Transcription factor	AD	<1	Waardenburg's syndrome type 4	Unknown

*Limited data available.

† No mutations detected thus far in humans, but associated with HD in mice.

AD, autosomal dominant; AR, autosomal recessive; CCHS, congenital central hypoventilation syndrome (Ondine's curse); ECE-1, endothelin-converting enzyme-1; EDNRB, endothelin receptor B; EDN3, endothelin-3; GDNF, glial cell line-derived neurotrophic factor; GFRα-1, GDNF family receptor α-1; HD, Hirschsprung's disease; L-HD, long-segment HD; MEN, multiple endocrine neoplasia; NTN, *neurturin*; RET, rearranged during transfection; S-HD, short-segment HD; SOX, Sry-like HMG bOX.

disorder relevant to pediatric surgery is hypertrophic pyloric stenosis (HPS). The genetic cause of HPS has long been recognized, with frequent familial aggregation, a concordance rate of 25% to 40% in monogenetic twins, a recurrence rate of 10% for males and 2% for females born after an affected child, and a ratio of risk of 18 for first-degree relatives compared with the general population.[46] However, this risk is considerably less than would be predicted based on mendelian patterns of inheritance.[10] In addition, HPS has been reported as an associated feature in multiple defined genetic syndromes,[9,35,36,59,67] chromosomal abnormalities,[12,27,29,60,70] and anecdotally with many other defects,[24,31,37,42,72] suggesting a polygenic basis. Although the molecular genetic basis of HPS remains poorly defined, a likely common final pathway causing the disorder is altered expression of neural nitric oxide synthase (nNOS) within the pyloric muscle.[51] A detailed analysis of the molecular mechanisms of this alteration has been published, describing a reduction of messenger RNA (mRNA) expression of nNOS exon 1c, with a compensatory up-regulation of nNOS exon 1f variant mRNA in HPS.[51] DNA samples of 16 HPS patients and 81 controls were analyzed for nNOS exon 1c promoter mutations and single nucleotide polymorphism (SNP). Sequencing of the 5′-flanking region of exon 1c revealed mutations in 3 of 16 HPS tissues, whereas 81 controls showed the wild-type sequence exclusively. Carriers of the A allele of a previously uncharacterized nNOS exon 1c promoter SNP (-84G/A SNP) had an increased risk of developing HPS (odds ratio, 8.0; 95% confidence interval, 2.5 to 25.6), which could indicate that the -84G/A promoter SNP alters expression of nNOS exon 1c or is in linkage dysequilibrium with a functionally important sequence variant elsewhere in the nNOS transcription unit and therefore may serve as an informative marker for a functionally important genetic alteration. The observed correlation of the -84G/A SNP with an increased risk for the development of HPS is consistent with a report showing a strong correlation of a microsatellite polymorphism in the *nNOS* gene with a familial form of HPS.[13] However, the -84G/A SNP does not account for all HPS cases; therefore, other components of the nitric oxide–dependent signal transduction pathway or additional mechanisms and genes may be involved in the pathogenesis of HPS. This is in accordance with other observations suggesting a multifactorial cause of HPS.[46] In summary, genetic alterations in the nNOS exon 1c regulatory region influence expression of the *nNOS* gene and may contribute to the pathogenesis of HPS, but there are likely numerous other genes that contribute to the development of HPS as well as predispose to environmental influences in this disorder.

These examples provide insight into the complexity of current models of molecular genetics and illustrate the inadequacy of current methods of analysis to fully define genetic causes of disease, particularly polygenic disorders. The majority of pediatric surgical disorders currently fall into the category of undefined multifactorial inheritance, which is even less well understood than the genetic categories described. In these disorders, no causative, predisposing, or influencing gene loci have been identified. Isolated regional malformations are presumed to result from interactions between the environment and the actions of multiple genes. Multifactorial inheritance is characterized by the presence of a greater number of risk genes within a family. The presumption of a genetic basis of the anomalies is based on recurrence risk. The recurrence risks in multifactorial inheritance disorders, although generally low, are higher than in the general population; they are increased further if more than one family member is affected, if there are more severe malformations in the proband, or if the parents are closely related. Beyond these generalizations, genetics can provide little specific information about this category of disorder.

Utility of Molecular Genetics in Clinical Pediatric Surgery

Genetic Counseling and Prenatal Diagnosis

As mentioned earlier, there is still a gap between genotypic understanding of a disorder and direct application to clinical treatment. The exceptions are in the areas of genetic counseling and prenatal diagnosis. Pediatric surgeons are likely to require some knowledge of molecular genetics as their role in prenatal counseling of parents continues to increase. Molecular genetics can supply specific information about an affected fetus by providing genotypic confirmation of a phenotypic abnormality, a phenotypic correlate for a confirmed genotype, and, in many instances, the recurrence risk for subsequent pregnancies and the need for concern (or lack thereof) about other family members. Once again, HD is an example of how molecular genetics can be valuable in genetic counseling.[8,64] The generalized risk to siblings is 4% and increases as the length of involved segment increases. In HD associated with known syndromes, genetic counseling may focus more on prognosis related to the syndrome than on recurrence risk. In isolated HD, a more precise risk table can be created. Risk of recurrence of the disease is greater in relatives of an affected female than of an affected male. Risk of recurrence is also greater in relatives of an individual with long-segment compared with short-segment disease. For example, the recurrence risk in a sibling of a female with aganglionosis beginning proximal to the splenic flexure is approximately 23% for a male and 18% for a female, whereas the recurrence risk in a sibling of a male with aganglionosis beginning proximal to the splenic flexure is approximately 11% for a male and 8% for a female. These risks fall to 6% and lower for siblings of an individual with short-segment disease. Prenatal diagnosis is possible if the mutation within the family is known. However, because the penetrance of single gene mutations is low (except for *SOX10* mutations in Waardenburg's syndrome), the clinical usefulness of prenatal diagnosis is limited.

More commonly, a general knowledge of genetics can allow accurate counseling of recurrence risk and reassurance for parents of an affected fetus diagnosed with a multifactorial inheritance defect, the most common circumstance involving prenatal consultation with a

pediatric surgeon. Pediatric surgeons should also be aware of the value of genetic evaluation of abortus tissue in cases of multiple anomalies when, after counseling, the parents choose to terminate the pregnancy. It is a disservice to the family not to send the fetus to an appropriate center for a detailed gross examination and a state-of-the-art molecular genetic assessment when appropriate.

As molecular genetics increasingly characterizes the genes responsible for specific disorders, their predisposing and modifier loci, and other genetic interactions, a better ability to predict the presence and severity of specific phenotypes will inevitably follow. This will allow prenatal counseling to be tailored to the specific fetus and lead to improved prognostic accuracy, giving parents the opportunity to make more informed prenatal choices.

Postnatal Treatment

In the future, molecular genetics will allow specific therapies to be optimized for individual patients. This may range from specific pharmacologic treatments for individual patients based on genotype and predicted pharmacologic response to anticipation of propensities for specific postoperative complications, such as infection or postoperative stress response. Of course, the ultimate treatment for an affected individual and their progeny would be to correct the germline genetic alteration responsible for a specific phenotype. Although there are many scientific and ethical obstacles to overcome before considering such therapy, it is conceivable that a combination of molecular genetics and gene transfer technologies could correct a germline mutation, replacing an abnormal gene by the integration of a normal gene and providing the ultimate preventive therapy. Although the state of gene transfer technology is far from this level of sophistication, progress in the past 3 decades can only be described as astounding. The next section provides an overview of the current state of gene transfer and its potential application for therapy.

GENE THERAPY

Gene therapy continues to be embroiled in controversy, its seemingly unlimited potential obscured by repeated disappointments and, more recently, adverse events. The year 2000 brought the first clinical gene therapy success—treatment of X-linked severe combined immune deficiency (XSCID)[11]—only to have this dramatic achievement undermined by the occurrence of leukemia in two patients. This and other adverse events threaten to overshadow the substantial progress made in gene transfer technology in recent years. Slowly but surely, methods for gene transfer are being developed that will have greater safety, specificity, and efficacy than ever before. Although complex issues remain to be solved, it is likely that successful gene therapy strategies will be developed and proved within the next few years. The technology of gene transfer can be divided into viral vector-based gene transfer and nonviral gene transfer. Because of the limited scope of this chapter and the limited efficiency of nonviral-based gene transfer thus far, only the current state of viral-based gene transfer is reviewed.

Viral Vectors for Gene Transfer

Viruses are highly evolved biologic machines that efficiently penetrate hostile host cells and exploit the host's cellular machinery to facilitate their replication. Ideally, viral vectors harness the viral infection pathway but avoid the subsequent replicative expression of viral genes that causes toxicity. This is traditionally achieved by deleting some or all of the coding regions from the viral genome but leaving intact those sequences that are needed for the vector function, such as elements required for the packaging of viral DNA into virus capsid or the integration of vector DNA into host chromatin. The chosen expression cassette is then cloned into the viral backbone in place of those sequences that were deleted. The deleted genes encoding proteins involved in replication or capsid or envelope proteins are included in a separate packaging construct. The vector genome and packaging construct are then cotransfected into packaging cells to produce recombinant vector particles (Fig. 2-3).

Given the diversity of therapeutic strategies and disease targets involving gene transfer, it is not surprising that a large number of vector systems have been devised. Although there is no single vector suitable for all applications, certain characteristics are desirable for all vectors if they are to be clinically useful: (1) the ability to be reproducibly and stably propagated, (2) the ability to be purified to high titers, (3) the ability to mediate targeted delivery (i.e., to avoid widespread vector dissemination), and (4) the ability to achieve gene delivery and expression without harmful side effects. There are presently five main classes of vectors that, at least under specific circumstances, satisfy these requirements: oncoretroviruses, lentiviruses, adeno-associated viruses (AAVs), adenoviruses, and herpesviruses. Table 2-2 compares the general characteristics of these vectors.

Oncoretroviruses and lentiviruses are "integrating," that is, they insert their genomes into the host cellular chromatin. Thus, they share the advantage of persistent gene expression. Nonintegrating viruses can achieve persistent gene expression in nondividing cells, but integrating vectors are the tools of choice if stable genetic alteration needs to be maintained in dividing cells. It is important to note, however, that stable transcription is not guaranteed by integration and that transgene expression from integrated viral genomes can be silenced over time.[53] Oncoretroviruses and lentiviruses differ in their ability to penetrate an intact nuclear membrane. Whereas retroviruses can transduce only dividing cells, lentiviruses can naturally penetrate nuclear membranes and can transduce nondividing cells, making them particularly useful for stem cell targeting applications.[19,74] Because of this difference, lentivirus vectors are superseding retrovirus vectors for most applications. Both types of vector, because of their ability to integrate, share the potential hazard of alteration of the host cell genome.

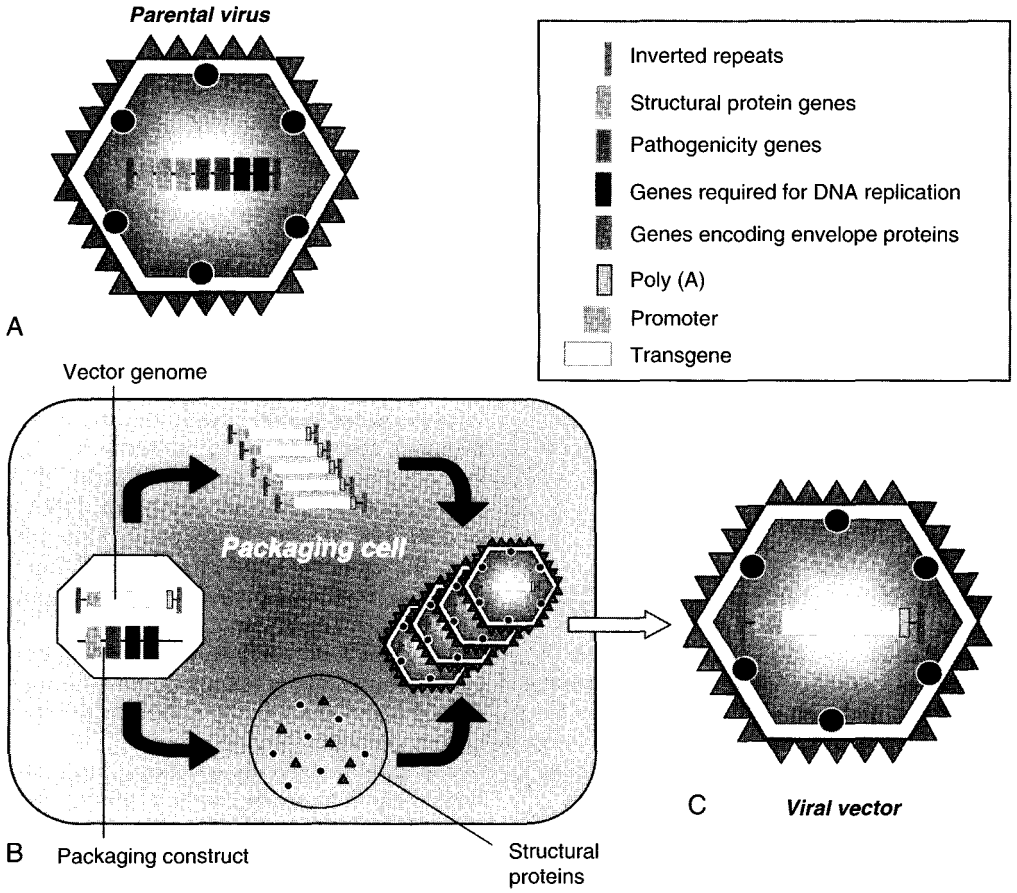


Figure 2-3 Requirements for the creation of a generic viral vector. *A*, The basic machinery of a chosen parental virus is used, including genes encoding specific structural protein genes, envelope proteins, and proteins required for DNA replication, but not genes encoding proteins conferring pathogenicity. *B*, The vector is assembled in a packaging cell. A packaging (helper) construct, containing genes derived from the parental virus, can be delivered as a plasmid or helper virus or stably integrated into the chromatin of the packaging cell. Pathogenicity functions and sequences required for encapsidation are eliminated from the helper construct so that it cannot be packaged into a viral particle. In contrast, the vector genome contains the transgenic expression cassette flanked by inverted terminal repeats and *cis*-acting sequences that are required for genome encapsidation. Viral structural proteins and proteins required for replication of the vector DNA are expressed from the packaging construct, and the replicated vector genomes are packaged into the virus particles. *C*, The viral vector particles are released from the packaging cell and contain only the vector genome. (*See color plate.*)

This could lead to the undesirable complications of human germline alteration or insertional mutagenesis, particularly important considerations for pediatric or fetal gene therapy.[56] Nevertheless, these vectors have proved most efficient for long-term gene transfer into cells in rapidly proliferative tissues and for stem cell–directed gene transfer.

Nonintegrating vectors include adenovirus, AAV, and herpesvirus vectors. Adenovirus vectors have the advantages of broad tropism, moderate packaging capacity, and high efficiency, but they carry the usually undesirable properties of high immunogenicity and consequent short duration of gene expression. Modifications of adenovirus vectors to reduce immunogenicity and further increase the transgene capacity have consisted primarily of deletion of "early" (E1–E4) viral genes that encode immunogenic viral proteins responsible for the cytotoxic immune response.[3,38] The most important advance, however, has been the development of helper-dependent adenoviruses (HD-Ads) that are deleted of all viral genes, thus eliminating the immune response to adenoviral-associated proteins.[48] These vectors may ultimately be most valuable for long-term gene transfer in tissues with very low rates of cell division, such as muscle or brain.

AAV is a helper-dependent parvovirus that, in the presence of adenovirus or herpesvirus infection, undergoes a productive replication cycle. AAV vectors are single-strand DNA vectors and represent one of the most promising vector systems for safe long-term gene transfer and expression in nonproliferating tissues. AAV is the only vector system for which the wild-type virus has no known human pathogenicity, adding to its safety profile. In addition, the small size and simplicity of the vector particle make systemic administration of high doses of vector possible without eliciting an acute inflammatory response or other toxicity. Although the majority of the

TABLE 2–2 Five Main Viral Vector Groups

Vector Type	Coding Material	Packaging Capacity (kb)	Tissue Tropism	Vector Genome	Advantages	Disadvantages
Retrovirus	RNA	8	Only dividing cells	Integrated	Persistent gene transfer in dividing cells	Requires cell division; may induce oncogenesis
Lentivirus	RNA	8	Broad, including stem cells	Integrated	Integrates into nondividing cells; persistent gene transfer	Potential for oncogenesis
HSV-1	dsDNA	40	Neural	Episomal	Inflammatory response; limited tropism	Large packaging capacity; strong tropism for neurons
AAV	ssDNA	<5	Broad	Episomal (90%) Integrated (<10%)	Noninflammatory; nonpathogenic	Small packaging capacity
Adenovirus	dsDNA	8 30*	Broad	Episomal	Extremely efficient gene transfer in most tissues	Capsid-mediated potent immune response; transient expression in dividing cells

*Helper dependent.

AAV, adeno-associated vector; ds, double-strand; HSV-1; herpes simplex virus-1; ss, single-strand.

AAV vector genome after transduction remains episomal, an approximately 10% rate of integration has been observed.[50] There are two primary limitations of AAV vectors. The first is the need to convert a single-strand DNA genome into a double strand, limiting the efficiency of transduction. Recently this obstacle has been overcome by the development of double-strand vectors that exploit a hairpin intermediate of the AAV replication cycle.[43] Although these vectors can mediate a 10- to 100-fold increase in transgene expression in vitro and in vivo, they can package only 2.4 kb of double-strand DNA, limiting their therapeutic usefulness. This relates to the second primary limitation of AAV vectors, which is limited packaging capacity (4.8 kb of single-strand DNA). One approach to address this limitation is to split the expression cassette across two vectors, exploiting the in vivo concatemerization of rAAV genomes. This results in reconstitution of a functional cassette after concatemerization in the cell nucleus.[17,49] Finally, an approach that has become common for enhancing or redirecting the tissue tropism of AAV vectors is to pseudotype the vectors with capsid proteins from alternative serotypes of AAV.[58] Although most rAAV vectors have been derived from AAV2, eight distinct AAV serotypes have been identified thus far, all of which differ in efficiency for transduction of specific cell types. AAV vectors have proved particularly useful for muscle, liver, and central nervous system directed gene transfer.

Herpes simplex virus (HSV-1) vectors are the largest and most complex of all currently used vector systems. Their primary advantages are a very large packaging capacity (up to 40 kb) and their strong neurotropism, allowing lifelong expression in sensory neurons. This has made neuropathologic disorders a primary target for HSV-1-mediated gene transfer.

Clinically Relevant Challenges in Gene Transfer

Recent adverse events demonstrate the potential for disaster when using vector-based gene transfer. Major initiatives must be undertaken to delineate the potential complications of gene transfer with specific vectors to convince physicians and the public of their safety for future clinical trials. Nevertheless, because of the potential benefit, continued efforts to develop safe and efficacious strategies for clinical gene transfer are warranted.

One of the primary obstacles to successful gene therapy continues to be the host immune response. The intact immune system is highly capable of activation against viral vectors using the same defense systems that combat wild-type infections. Viral products or new transgene encoded proteins are recognized as foreign and are capable of activating an immune response of variable intensity. Adenovirus vectors are the most immunogenic of all the viral vector types and induce multiple components of the immune response, including cytotoxic T-lymphocyte responses, humoral virus-neutralizing responses, and potent cytokine-mediated inflammatory responses.[7] Great progress has been made in reducing T-cell responses against adenoviral antigens by the development of HD-Ad vectors that are deleted of all adenoviral genes. These vectors have demonstrated reduced immunogenicity with long-term phenotypic correction of mouse models and negligible toxicity.[14,34] However, even HD-Ad vectors or less immunogenic vector systems such as AAV or lentivirus vectors can induce an immunologic response to capsid proteins or to novel transgene encoded proteins, a potentially limiting problem in a large number of human protein deficiency disorders caused by a null mutation. Thus, the application of gene transfer technology to many human disorders may

require the development of effective and nontoxic strategies for tolerance induction.

Another major area of interest that may improve the safety profile of future viral vector-based gene transfer is specific targeting to affected tissues or organs. Whereas wild-type virus infections are generally restricted to those tissues that are accessible through the route of transmission, recombinant vectors are not subject to the same physical limitations. The promiscuity of viral vectors is a significant liability, because systemic or even local administration of a vector may lead to unwanted vector uptake by many different cell types in multiple organs. For instance, lack of adenovirus vector specificity was directly linked to the induction of a massive systemic immune response that resulted in a gene therapy–related death in 1999.[7] Because many of the toxic effects of viral vector-based gene transfer are directly related to dose, increasing the efficiency with which viral vectors infect specific cell populations should reduce viral load and improve safety.

There are a variety of promising methods to achieve the targeting of viral vectors for specific organs or cell types. Perhaps the simplest approach is vector pseudotyping, which has been performed for retrovirus, lentivirus, and AAV vectors. By changing the capsid envelope proteins to alternative viral types or serotypes, a portfolio of vectors with different tropisms can be generated.[40] Another approach is the conjugation of capsid proteins to molecular adapters such as bispecific antibodies with specific receptor binding properties.[33,61] A third approach is to genetically engineer the capsid proteins themselves to alter their receptor binding (i.e., to abolish their normal receptor binding) or to encode a small peptide ligand for an alternative receptor.[28] These and other approaches, when combined with the appropriate use of tissue-specific promoters, may significantly reduce the likelihood of toxicity from viral-based gene therapy.

Another important obstacle to human gene therapy—particularly fetal gene therapy—is the potential for insertional mutagenesis when using integrating vectors. Until recently, this risk was considered extremely low to negligible, based on the assumption that oncogenesis requires multiple genetic lesions and the fact that induced cancer had not been observed in any of the hundreds of patients treated with retrovirus vectors in the many gene therapy trials. However, recently 2 of 11 patients treated in an otherwise successful trial[11,25] of retroviral gene therapy for XSCID developed a leukemia disorder.[26] Evidence suggests that this was caused by retroviral genome insertion in or near the oncogene *LM02*. These concerns have been further heightened by evidence that retroviral genes are not randomly inserted, as previously believed; rather, they preferentially integrate into transcriptionally active genes.[65] Although such events may be more likely to occur under the unique selective influences of XSCID, it is clear that the risk of insertional mutagenesis can no longer be ignored. Approaches designed to neutralize cells expressing transgene if and when an adverse event occurs, such as engineering suicide genes into the vector, are one option, but this would also neutralize any therapeutic effect. More exciting approaches are based on site-specific integration—for instance, taking advantage of site-integration machinery of bacteriophage ϕX31.[52] This is undoubtedly only one of many approaches that will use site-specific integration in the future and should, if successful, negate the risk of insertional mutagenesis.

Finally, a critical issue for in vivo gene transfer with integrating vectors in individuals of reproductive age is the potential for germline transmission, with alteration of the human genome. The risk of this event is poorly defined at present and is most likely extremely low, although in some circumstances (e.g., fetal gene transfer), it could be increased.[56] Although still not technically possible, the intentional site-specific correction of defects in the germline would be the ultimate in gene therapy. However, even if the technology becomes available, the intentional alteration of the human genome raises profound ethical and societal questions that will need to be thoroughly addressed before its application. The considerations are similar to those for insertional mutagenesis, so many of the approaches mentioned earlier for gene targeting and reduction of the potential for insertional mutagenesis are applicable here as well.

Overview of the Current Status of Gene Transfer

At present it is clear that viral vectors are the best available vehicle for efficient gene transfer into most tissues. Several gene therapy applications have shown promise in early-phase clinical trials. Although the adverse events noted in the XSCID trial have dampened enthusiasm, this still represents the first successful treatment of a disease by gene therapy. The treatment of hemophilia B using rAAV is also promising.[32,41] The next few years are likely to bring advances in the treatment of certain types of cancer using conditionally replicating oncolytic viruses and in the treatment of vascular and coronary artery disease using viral vectors that express angiogenic factors. In the future, new disease targets are likely to become approachable through the fusion of viral vector-mediated gene transfer with other technologies such as RNA interference, a powerful tool to achieve gene silencing. Such vectors could be useful in developing therapy for a range of diseases, such as dominantly inherited genetic disorders, infectious diseases, and cancer. Advances in the understanding of viral vector technology and DNA entry into cells and nuclei will likely lead to the development of more efficient nonviral vector systems that may rival viral vectors in efficiency and have superior safety. Gene vector systems of the future may be very different from those in use today and will ultimately provide efficient delivery of target-specific, regulated, transgene expression for an appropriate length of time.

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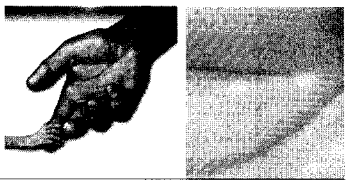
Chapter 3



The Impact of Tissue Engineering in Pediatric Surgery

Tracy C. Grikscheit and Joseph P. Vacanti

Extirpative surgery often requires reconstruction to replace the purpose and appearance of the excised tissue. In the case of congenital defects, a tissue deficit may already exist. The goal of tissue engineering and organ fabrication is to create living replacement organs and tissues, with the proposed advantages of more exact replacement and better durability related to cellular proliferation and autologous repair. These techniques are beginning to make the transition from the laboratory to the operating room, providing a better proxy for appearance and function in patients affected by congenital anomalies or resection.

Early attempts by surgeons to substitute for either function or cosmesis include those detailed in the *Sushruta Samhita* from around 6 BC, describing rhinoplasty using a forehead flap, and various wooden and metal prostheses mentioned in the Talmud. Modern progress has embraced both these approaches, developing multiple procedures that rely on either the substitution of tissues, as in the transfer of a toe to replace a finger, or the use of a manufactured substitute such as Dacron aortic grafts. The limitations of native substitution lie in the dilemma of prioritizing the value of various tissues and the trade-off that must be made. In pediatric surgery, there is a fairly limited supply of donor tissue that remains inherently different from the tissue it replaces. Manufactured substitution also has acknowledged problems: material failure, increased rates of infection, and the immune system's destruction of foreign material. In addition, nonliving material does not grow with the patient or adapt to changing circumstances, so pediatric patients may need to undergo multiple operations with increasing levels of complexity. Neither approach can solve the replacement of composite tissues.

Organ transplantation, a modern version of native tissue substitution, has demonstrated that functional replacement can be lifesaving, but there are obstacles, including a limited supply and a long list of associated morbidities.

The resilience of surgical therapy is of particular concern in pediatric surgery, where the surgical outcome may be measured over decades and the surgical reconstruction is subjected to higher levels of activity and physiologic change. In addition, in some congenital defects, the amount of available donor tissue may be insufficient, and prosthetic material may not approximate the functional and cosmetic requirements of the missing tissue, including growth.

Solutions to problems in the surgical treatment of children with short-bowel syndrome, craniofacial defects, and congenital heart defects are imminent. Human application of tissue-engineered skin and cartilage has already occurred. We look forward to significant advances in vascular substitutes and intestinal replacement and progress with the solid organs, which have proved to be the most elaborate systems to replicate.

TECHNIQUES AND PRINCIPLES OF TISSUE ENGINEERING

Monolayer cell culture is a well-defined science, but organizing cell combinations into complex, three-dimensional functional structures relies on numerous relationships between the structure given to the cells and the cells assembled on the structure. After defining the cellular components and the structure of the engineered organ, adding adequate vascularization and directing the symphony of cell signaling found in normal tissues are the greatest challenges.

The manifold approaches to tissue engineering can be broadly reduced to in vitro and in vivo designs. All have attempted to provide an underlying support or scaffold for the cells, a proper population of cells, and a substitute for the extracellular matrix. Interactions between cells and extracellular matrix require cell migration, proliferation, differentiation, and apoptosis, which are all critical functions for a tissue-engineered construct.[60]

In vitro models have usually relied on the formation of a bioreactor system or cell patterning for monolayer

co-culture studies.[20,42,58,101] Bioreactors are dynamic tissue culture devices that range from simple mechanical designs to more complex systems with oxygen exchange, defined flow rates, and electrical and mechanical stimulation. The tissue engineering of less complex tissues such as cell sheets requires only a simple method of exchange of growth medium to the engineered construct that avoids stasis. Spinner flasks or rotating vessels are examples.[22]

More complex bioreactors have been designed to furnish stretch to skeletal muscle cultures,[94] shear to endothelial cells,[96] and compression to chondrocytes.[12] There is good evidence that cell-polymer constructs grown in vitro under physiologic conditions that are closer to those found in vivo, including strain and pericellular nutrient flow, result in improved cell morphology, growth characteristics, and metabolic activity.[55,68,81] Studies of chondrocytes grown on polyglycolic acid constructs in cultures subjected to hydrodynamic forces show that cell proliferation rates are nearly 50% greater, there are 60% more glycosaminoglycans, and 125% more collagen in the extracellular matrix is regenerated.[4,32]

Other in vitro models for tissue engineering include cell patterning in either monolayer or three-dimensional culture. Defined tissue architectures yield more predictable patterns of growth and differentiation. In the case of more complex organs, such as the liver, co-culture in tissue-specific media is emerging as a necessity for successful designs.[5] Photolithography has been used to generate alternating domains of *N*-(2-aminoethyl)-3-aminopropyl-trimethoxysilane and dimethyldichlorosilane to preferentially seed human bone-derived cells to the former domains, mediated through vitronectin.[58] High-resolution patterns of poly-L-lysine were used in micrometer scale microcontact printing to align cultured neurons,[42] adhered via microcontact printing of specific oligopeptides.[101] Constraint of cell spreading and nonrandom co-cultures of cells more closely replicate the three-dimensional organized architecture of human tissues.[58] Topographic cues may be just as important as some biologic signals.

A highly promising intersection of microfabrication engineering and improved in vitro tissue culture systems is resulting in the development of smaller, smarter bioreactors in which microfluidics, mass transfer, nutrition extraction, and cell growth can all be studied with known cellular architecture and standardized microfabrication to the micrometer scale.[8,9,20,44] As described later in the section on tissue engineering of the liver, this approach may be critical for complex organs.

In vivo studies have used animals as a complex bioreactor, with composite constructs implanted into vascularized spaces such as the omentum, mesentery, interscapular fat pad, or latissimus dorsi, where an endogenous blood supply can participate in angiogenesis.[93] A substitute for the extracellular matrix in the form of a scaffold is implanted after cell loading onto the construct.[52] Prevascularization of polymer sponges, by implanting a construct days to weeks before adding cells, can increase cell survival rates.[87]

In one of the earlier in vivo models, liver, intestine, and pancreas parenchymal cells were implanted on biodegradable polymers after 4 days of in vitro culture, resulting in viable cells, mitotic figures, and vascularization of the growing cell mass.[93] One polymer used in this report was a 90-10 copolymer of glycolide and lactide, produced commercially as Vicryl. With the recent explosion of available biomaterials, researchers have successfully used an increasing variety of scaffolds, including small intestinal submucosa as a small-caliber venous graft with hepatocyte transplantation, anastomosed between the portal vein and the inferior vena cava.[49] Additional success with calcium alginate gels, commercially available surfactants, agarose, fibrin glue, and microfabricated biodegradable materials illustrates the necessity of collaboration between chemical and tissue engineers.[1,35,36,95]

A combination of in vitro and in vivo approaches has solved some simple tissue engineering problems and will continue to be important for autologous tissue removal, augmentation in the laboratory, and eventual in vivo replacement.

CARTILAGE AND BONE TISSUE ENGINEERING

Structural defects characterize many congenital and acquired problems encountered by pediatric surgeons. Some pioneering treatments have capitalized on in situ tissue engineering, such as distraction osteogenesis followed by bone grafting to treat Treacher Collins syndrome.[57] In the 1960s, Tessier performed wide mobilization of large segments of the skull and translocation of the eyes in the case of Apert and Crouzon syndromes.[83]

To supplement these pioneering approaches, tissue engineers have sought to generate greater quantities of bone and cartilage. This began with the observation that chondrocytes harvested from the articular surfaces differentiated in culture to cartilage, whereas chondrocytes from periosteum initially resembled cartilage but progressed in culture to form new bone.[92]

A relatively simple tissue, cartilage has a limited spontaneous regenerative capacity after destruction.[24,26,59] Repair of major articular cartilaginous defects occurs through the formation of fibrocartilaginous tissue, with a different biochemistry and biomechanical profile from native cartilage.[39] Osteoarthritis with pain and decreased function can result from inadequate repair.[18] In 1988 Vacanti et al. produced new hyaline cartilage from bovine chondrocytes on a polymer scaffold.[90]

In subsequent studies using nonwoven polyglycolic acid mesh or copolymers of polyglycolic acid and polylactic acid, the constructs could be made into predetermined shapes.[90] This led to the formation of cartilage in the shape of a human ear[88] and a temporomandibular joint disk,[66] as well as cartilage shaped specifically to substitute for worn articular cartilage in meniscus replacement.[38] Tissue-engineered cartilage has also been used as a structural mass for nipple reconstruction in pigs[14] and to close cranial defects in animals.[53] Cartilaginous tubes lined with respiratory epithelium have been produced and implanted as a tracheal replacement,[69,91] and formed cilia were seen on some epithelial cells at 3 weeks.[69]

The tissue engineering of bone originated in cartilage tissue engineering, with the transfer of bovine periosteal cells to polyglycolic acid scaffolds and implantation into

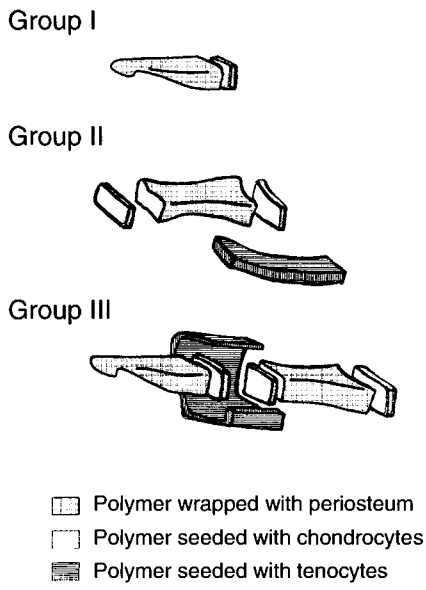


Figure 3–1 Three different types of composite tissue structures composing a tissue-engineered finger. The structures were constituted in vitro by suturing to create models of a distal phalanx (Group I), a middle phalanx (Group II), and a distal interphalangeal joint (Group III). The sutured tissues were then implanted subcutaneously in athymic mice. (From Isogai N, Landis W, Kim TH, et al: Formation of phalanges and small joints by tissue-engineering. J Bone Joint Surg Am 1999;81:306-316.)

athymic mice. These constructs stained for osteocalcin and showed focal points of bone formation on microscopic evaluation. These constructs were then implanted to repair parietal, frontal, and temporal cranial bone defects in nude rats; polymer without cells was used as a control.[89] Bony repair with the tissue-engineered constructs was observed, compared with no change in the cranial defects in the control group. Similarly, this technique has been applied to femoral shaft defects fixed with plates to maintain a critical gap. Nonunion was observed in the control group, and exuberant callus formation was seen in the tissue-engineered group.

A combination of tissue-engineered bone and cartilage has been used to create a finger replacement.[41] Three types of bovine cells—periosteum, chondrocytes, and tenocytes—seeded on copolymers of polyglycolic acid and poly-L-lactic acid formed a composite tissue resembling a joint (Fig. 3-1). The parts were assembled and sutured together in the form of a distal phalanx, middle phalanx, and distal interphalangeal joint. This assembly was then implanted subcutaneously in athymic mice. At 20 weeks, the shape and histology of a human phalange with a joint were preserved, with mature articular cartilage, subchondral bone, and a tenocapsule. Bone and cartilage tissue engineering is promising for joint reconstruction and to address the complex congenital anomalies that pediatric orthopedic surgeons must contend with.

CARDIOVASCULAR TISSUE ENGINEERING

Each year in the United States 5 to 8 of every 1000 live births result in a child with congenital cardiac malformations, including valvular disorders.[17] Pediatric surgical treatment of congenital heart defects commonly requires nonautologous conduits or valves.[56,71] In the early 1960s more than 40% of valve replacements were composed of bovine or porcine tissue preserved by glutaraldehyde.[71] Tissue replacement valves avoid the problems of mechanical valves, including systemic thromboembolism and thrombotic occlusion,[21] but they still have a 50% to 60% reoperation rate at 10 years for prosthesis-associated problems, including structural and nonstructural dysfunction, progressive deterioration (calcific and noncalcific), and infection.[21,33] Additionally, the most commonly used replacement tissue valves have limited durability due to progressive deterioration.[71]

The perfect replacement valve would be a nonobstructive, nonthrombotic, self-repairing tissue valve that grows with the patient and remodels in response to in vivo stimuli.[71] These criteria are unchanged from those originally outlined by Harken et al. in 1962.[34] A one-time repair would be invaluable for pediatric patients, who currently may require numerous operations over a lifetime.

The tissue-engineered heart valve has been approached using traditional methods of tissue engineering. Seeded cells on a scaffold construct were tried first with a decellularized xenogeneic valve, then later on pure polymer molded to the proper form.[2,62,72] In the first studies, human endothelial cells from the saphenous vein were seeded on porcine aortic valves treated with Triton detergent to remove the native cells and leave the extracellular matrix as the cellular support.[2] Implanted as pulmonary valve replacements in sheep, the valves were hemodynamically functional and showed no calcification at harvest.[2] Similar results were achieved with a composite bioprosthesis sutured from various leaflets and conduit, again decellularized before seeding.[62]

Engineering a polymer scaffold, rather than destroying the cells of an existing valve and repopulating it, was crucial to achieve a living valve that could possibly grow. As the autologous cells populate the polymer scaffold, which then biodegrades, the cells also secrete an extracellular matrix to retain mechanical strength.[76] Initial studies of polyglycolic acid scaffolds seeded with sheep endothelial cells and myofibroblasts, implanted after resection of the native right posterior leaflet of the pulmonary valve in sheep, resulted in no stenosis and appropriate cellular architecture and matrix formation.[72] When the implanted cells were labeled with a cellular marker, the leaflets increased collagen content and added elastin, and the original cells persisted, again with demonstrable valve function by echocardiography.[10]

The addition of mechanical bioreactors that increasingly stress the engineered valve and improved polymer scaffolds (polyhydroxyalkanoate) resulted in a pulmonary valve with minimal regurgitation, no thrombus formation, laminated fibrous tissue, and increased extracellular matrix.[76] Engineered valves grown under mechanical stress with approximated systolic pulse pressure[77] function in vivo for up to 5 months and resemble native valves in terms of matrix formation, histology, and biomechanics.

Although some of Harken's criteria have been met by the tissue-engineered valves, and the critical ability to grow with the host may be met as well, the valves need to be

tested and succeed in the aortic position, because this is the most frequently diseased, studied, and replaced valve.[71]

VASCULAR TISSUE ENGINEERING

In addition to valvular repair, a second factor in many pediatric congenital cardiac defects is the development of an adequate conduit, for which homografts or prosthetic materials have been used. These do not grow and functionally degenerate through calcification and tissue ingrowth, leading to multiple surgical replacements. Smaller vessels, those less than 6 mm, cannot be satisfactorily constructed from textile or expanded polytetrafluoroethylene (PTFE) and must be bypassed with autologous arteries and veins, with a limited supply for multiple operations.[86]

Given these drawbacks, tissue engineering is a logical strategy for small and large vessel replacements. In February 2001 the first human use of a tissue-engineered vessel was reported by Shin'oka et al. (Fig. 3-2) in a 4-year-old girl who had previously undergone a Fontan procedure and pulmonary artery angioplasty at age 3 years 3 months for a single right ventricle and pulmonary atresia.[73] Subsequent angiography revealed total occlusion of the right intermediate pulmonary artery. A 2-cm autologous segment of peripheral vein was harvested and its cells isolated and expanded in culture to 12×10^6 cells at 8 weeks. A tube of polycaprolactone and polylactic acid copolymer in a 1:1 weight ratio reinforced with woven polyglycolic acid served as a scaffold for the seeded cells, which were implanted 10 days after seeding to reconstruct the occluded pulmonary artery. After 7 months of follow-up, no complications were noted.

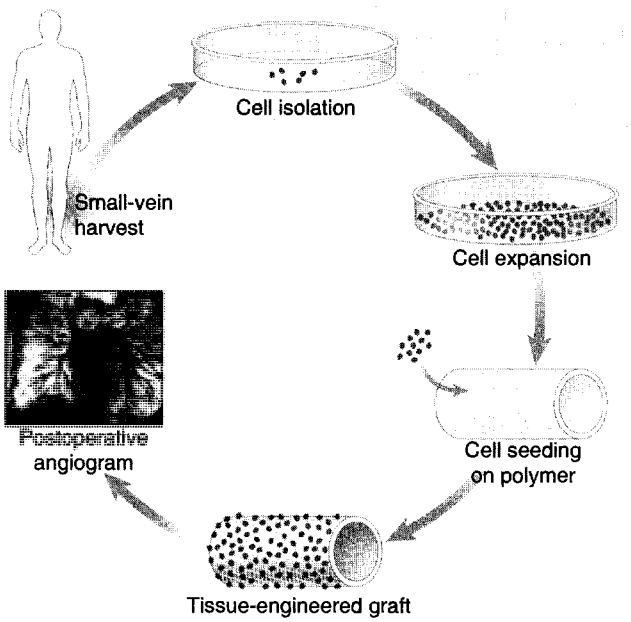


Figure 3–2 Basic tissue-engineering technique. Cells from native vein were isolated and expanded in vitro and seeded on a biodegradable polymer scaffold to form a tissue-engineered pulmonary artery that was subsequently implanted in a child, with good results. (From Shin'oka T, Imai Y, Ikada Y: Transplantation of a tissue engineered pulmonary artery [letter to the editor]. N Engl J Med 2001;344:532-533.)

Tissue engineering of the vasculature began in 1978, when Herring successfully isolated endothelial cells from veins and transplanted them on synthetic scaffolds.[98] Several scientists improved the function and architecture of the tissue by alternating seeding protocols, scaffold composition, and culture conditions. In 1998 Shin'oka et al. cultured ovine arterial and venous endothelial cells in similar conditions to the human replacement and replaced a 2-cm segment of pulmonary artery in lambs.[74] The acellular control was thrombosed, whereas the engineered tissue had a luminal endothelial layer, collagen, and elastin and was nonthrombosed at explant.[74] Similarly, a construct seeded with ovine venous cells on a different polymer (poly-4-hydroxybutyrate) and sutured to the pulmonary artery in patch augmentation resulted in increased proteoglycans, elastin, and collagen and remained patent.[78] Polyhydroxyalkanoate and polyglycolic acid copolymer seeded with ovine arterial cells also resulted in a patent patch graft, and the mechanical stress-strain curve began to approximate that of native vessel over time.[75]

Improved conduit strength, viability, and durability will likely develop with improved understanding of cell-cell and cell-polymer interactions, leading to the regeneration of an architecture that includes extracellular matrix, a smooth lining of endothelial cells at the luminal surface, and collagen and elastin fibers. Use of tissue fragments to seed constructs that contain multiple cell types, including bone marrow, has been reported to accelerate graft healing and preclude intimal hyperplasia.[61] Similarly, improvements in the polymer characteristics have enhanced the rate and quality of vessel development.[75,100]

INTESTINAL TISSUE ENGINEERING

Of the morbid conditions associated with bowel resection, short-bowel syndrome is the most devastating. It is characterized by progressive weight loss, malnutrition, vitamin deficiency, and infections associated with the vascular access commonly used to support patients with this syndrome.[99] Short-bowel syndrome typically ensues when less than one third of normal small intestine remains after massive resection or surgical treatment of a number of intestinal problems. Although there are some surgical innovations for the treatment of this syndrome, including bowel transplantation,[13] reversed segments,[19] recirculating loops,[84] and tapering and lengthening procedures to encourage intestinal mucosa to proliferate,[65,97] there is no perfect surgical solution. Intestinal transplantation has had some early success but is not widely available. Initial work in the tissue engineering of intestine included autologous patches of serosa or vascularized pedicles, which had mixed success.[7,51,54] This was also performed with patches consisting of polymer, AlloDerm, and SIS, the collagenous submucosa of the intestine.[3,15,40] Tissue engineering offers an attractive alternative with

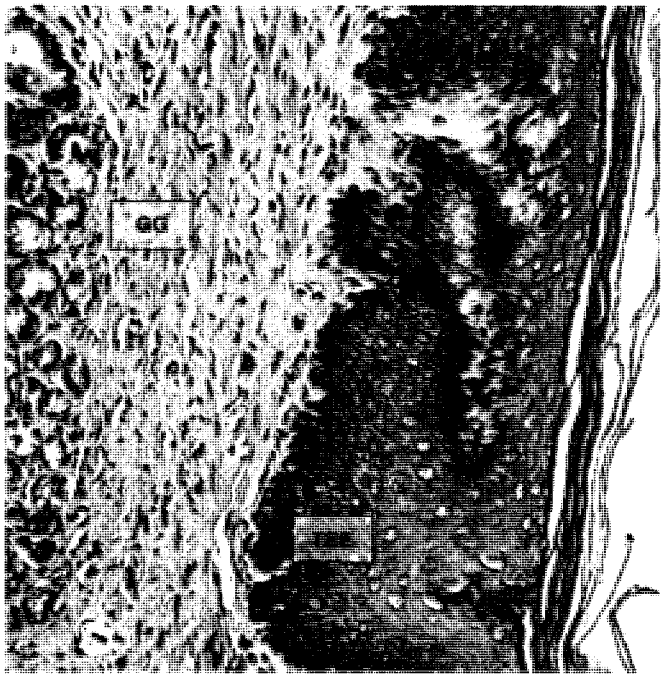


Figure 3–3 Tissue-engineered esophagus (TEE) at the gastroesophageal junction, with engineered esophagus (EE) and native stomach with gastric glands (GG) in close approximation. (From Grikscheit T, Ochoa ER, Srinivasan A, et al: Tissue-engineered esophagus: Experimental substitution by onlay patch or interposition. J Thorac Cardiovasc Surg 2003;126:537-544.)

the goal of replacing the intestine before establishing a connection to the native intestinal lumen.

Beginning with the observation that fetal intestine transplanted on polymer scaffolds showed proliferation and intestinal morphogenesis,[93] the production of tissue-engineered intestine has expanded in the rat model from small intestine alone to include engineered stomach, gastroesophageal junction, esophagus, and colon (Figs. 3-3 and 3-4).[27-29,31] The generation of a composite tissue resembling small intestine generated from intestinal cells heterotopically transplanted as organoid units was first reported in 1998.[16] Organoid units are taken from full-thickness harvests of intestine and purified through surgical dissection, enzymatic digestion, and trituration before differential centrifugation. Products from this preparation—the organoid units—are loaded on 2-mm nonwoven cylindrical polymers made of polyglycolic acid and coated with polylactic acid before implantation into the omentum. Although the implanted polymer initially must be subjected to a low oxygen tension, angiogenesis occurs. The growth of the engineered bowel reflects polarization of the epithelial cells to face inward toward the lumen of the cyst, with appropriate reconstitution of the other layers of the intestinal wall, including muscle and nerve. Substantial vascularization accompanies the growth.[16]

Long-term follow-up after anastomosis of tissue-engineered small intestine to native jejunum after 75% small bowel resection in male Lewis rats revealed weight gain, bowel patency, and statistically significant increases in the engineered intestine size.[45,48] When used as a "rescue" following massive small bowel resection, animals with tissue-engineered small intestine regained weight at a more rapid rate, up to their preoperative weights; animals without the engineered intestine foundered.[30] Investigation of the immune system of the anastomosed small bowel indicates that the neomucosal immune cell population is a function of exposure to luminal antigens and time of harvest.[64] In anastomosed tissue-engineered small intestinal mucosa harvested at 20 weeks, the density and topographic distribution of immune cell subsets were identical to that of normal jejunum. Epithelial messenger RNA expression topography of SGLT1, a bowel sodium-glucose cotransporter, is also regenerated in anastomosed engineered small intestine, as is DCT1, an iron transporter; however, vascular endothelial growth factor and basic fibroblast growth factor levels are different from those of native intestine.[25,82] The distribution patterns of these transporters indicate that the engineered intestine repeats the pattern of native jejunum,

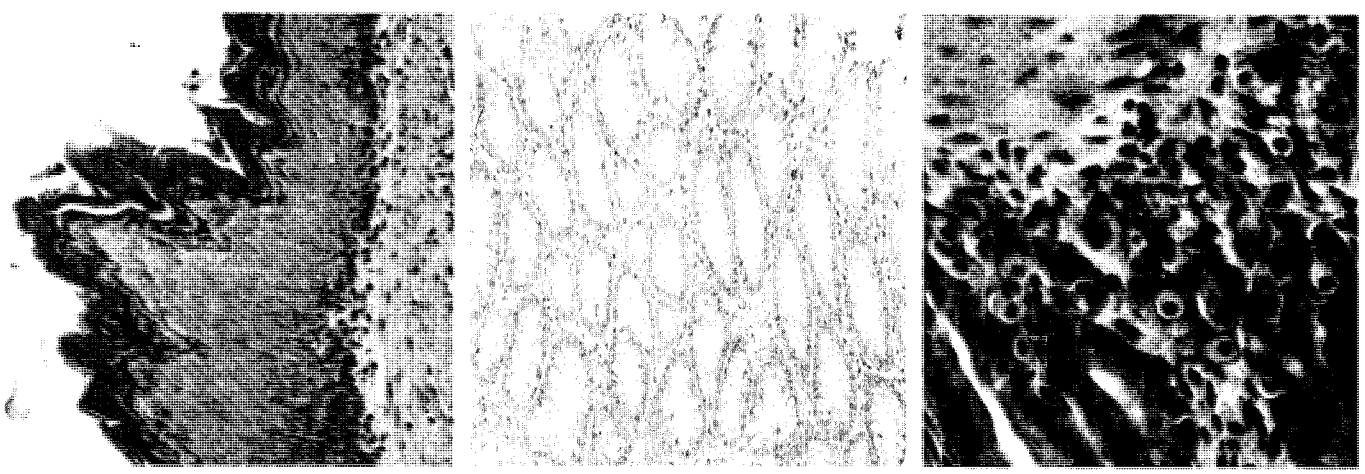


Figure 3–4 Tissues engineered in the Lewis rat model. *A*, Tissue-engineered esophagus (original magnification ×20). *B*, Tissue-engineered colon (original magnification ×20). *C*, Tissue-engineered stomach. Note the large lucent parietal cells and glandular structure. (Courtesy of Dr. T. Grikscheit.)

underlining the therapeutic potential of this conduit for patients who lack small bowels.

With refinements of the organoid protocol for engineered intestine, larger amounts have been created with larger surface areas, and engineered colon, stomach, and esophagus can be generated (see Fig. 3-3).[30] More than 20 times the volume of the implanted polymer can be produced.[27,30] Tissue-engineered colon functioned as a replacement in Lewis rats for 41 days, with maintenance of sodium levels, fluid absorption, generation of stool short-chain fatty acids, prolonged transit time, and architecture that included ganglion cells and authentic colon histology.[27,29] Tissue-engineered esophagus has been used both as a patch and as an interposition graft in rats in preliminary studies (see Fig. 3-3).[28] In the case of tissue-engineered stomach, the idea of exact replacement has been extended in a series of studies showing that a tissue-engineered gastroesophageal junction can be prepared, as well as an antrum alone, and either young or old rats can be the autologous donors.[31] The tissue stains appropriately for gastrin, has parietal cells, and has the exact architecture of native stomach. The tissue-engineered stomach can be labeled with a viral protein (green fluorescent protein) for later identification, opening the door for future transfections for "designer intestine"; for example, tissue-engineered colon could be transfected with SGLT1 to allow it to absorb sugars.[31]

Engineered intestinal replacement is central to the treatment of many critical pediatric surgical diseases and may significantly impact patient care in the coming decade, with improved surface area, transporter function, immune characteristics, and architecture. Large animal studies have begun in some laboratories, with the successful growth of a small amount of tissue-engineered small intestine and stomach in one.

LIVER REPLACEMENT AND TISSUE ENGINEERING

The liver is a complex and indispensable organ that provides vital functions, including metabolism, excretion, detoxification, storage, and phagocytosis. Global failure of this organ with acute or chronic liver dysfunction accounts for the death of 30,000 Americans each year, with acute failure mortality rates exceeding 80%.[85] Chronic failure is the sixth leading cause of death in the United States and ranks eighth in economic costs among major illnesses. Currently, the only definitive treatment for severe hepatic failure is orthotopic liver transplantation, with 3000 of these procedures performed annually. Attempts to tissue-engineer a liver for replacement have included direct cellular injection or transplantation on polymer constructs, with or without hepatotrophic stimulation; the development of extracorporeal bioartificial liver (BAL) devices; and new three-dimensional microfabricated constructs intended to be intracorporeal.

Tissue engineering of the liver initially began with cell transplantation after the observation that orthotopic liver transplantation might not be necessary when the replacement of selected populations of cells could treat the liver function deficiencies.[68] The Promethean regeneration of the liver made the idea of hepatocyte transplantation more attractive.

In early studies, when hepatocytes were injected into the portal veins of Gunn rats deficient in uridine diphosphate glucuronyltransferase, they maintained a lower bilirubin level than control animals injected with saline.[55] Hepatocyte injection into the portal vein or peritoneal cavity was performed after inducing liver failure with dimethylnitrosamine.[81] Rats that received the injection of hepatocytes lived significantly longer than those in the control group. Hepatocellular injections into the spleen, pancreas, and peritoneal cavity retained functional capacity in several studies and were also noted to migrate. Hepatitis B virus surface antigen–producing hepatocytes, introduced ectopically, were noted to migrate to the pancreas, lung, and spleen while maintaining function.[32] The limitation of this approach is the overall functional capacity of the injected cells, which decreases over time. Migration and attrition contribute to the failure to develop a discrete liver mass.

Tissue-engineered liver mass has increased by concurrent hepatotrophic stimulation and improved cellular selection. Hepatotrophic stimulation, which exists in patients with hepatic failure receiving tissue-engineered liver therapies, has been reproduced by partial hepatectomy, portacaval shunting, and injection of liver toxins. Following liver resection, it is well known that the remaining liver rapidly proliferates with multiple growth stimuli, including epidermal growth factor, hepatocyte growth factor, insulin, and glucagon.[11] The increased amounts of these factors in portal blood have led to the approach of portacaval shunting in host animals when tissue-engineered constructs are implanted into the mesentery or omentum, to give the construct a rich supply of trophic factors. Hepatectomy and portacaval shunting at the time of construct implantation result in increased proliferation of transplanted hepatocytes, longer cell survival, better organization, and higher levels of bilirubin clearance in Gunn rats.[46,70,87]

Cellular transplantation, even with maximal hepatotrophic stimulation, does not yet deliver adequate hepatocellular mass to detoxify the plasma of a human patient in fulminant hepatic failure. Therefore, a tissue-engineered liver may provide temporary liver function replacement in the form of an extracorporeal BAL device or, more recently, a microfabricated intracorporeal device. The goals of an extracorporeal BAL are to serve as a bridge to transplantation, reducing postoperative morbidity and mortality,[79] as well as to support acute liver failure patients while liver regeneration occurs or those who are ineligible for transplant secondary to concomitant disease.

Experimental models of rat, porcine, or human-derived hepatocyte cell lines in a tissue-engineered scaffold-cell combination have been used to detoxify the blood of patients in fulminant hepatic failure.[43,80] In a device that has undergone trials in human patients with hepatic failure, porcine hepatocytes bound to collagen-coated microcarriers in dialysis membranes are attached extracorporeally.[67]

Despite the development of stable hepatocyte culture systems, including collagen sandwich and double gel

systems, prolonged plasma exposure to the hepatocyte cultures in microfabricated bioreactors produces significant accumulations of intracellular triglyceride droplets, leading to a severe reduction in cellular function. The current life span of the BAL is hours to days, which must be improved for long-term therapy. In more recent investigations, co-cultured hepatocytes and nonparenchymal cells were more tolerant of the plasma milieu.[6]

The premise of co-culture in liver cell culture originated with the observation that mesenchymal cells of the umbilical and vitelline veins induce the endodermal "liver bud" to proliferate, branch, and differentiate in utero.[37] The adult liver provides a scaffold for many complex cell-cell interactions (biliary ductal, Kupffer, sinusoidal endothelial cells, and hepatocytes), which allow coordinated organ function. These interactions imply an essential role for cell signaling between mesenchymal and parenchymal tissue compartments.

The cellular physiology of the liver is complex, and the life span of mature hepatocytes, although lengthened with improvements in culture conditions, is measured in weeks.

Coupled with modern advances in microfabrication, observations about cellular co-culture may lead to an implantable tissue-engineered liver. Vascular ingrowth into transplanted constructs may never be adequate for a complex organ such as the liver, however. Therefore, our laboratory has sought to build a vascular system down to the level of the capillary itself, and then add the parenchyma of complex organs.[9] A de novo vascular system could be used as a template for any thick and complex tissue such as the heart, liver, or kidney, all of which rely on extensive vascularization, exceeding the limits of host ingrowth alone.[9]

Ordered arrays of channels for hepatocytes with regionally designed cell adhesion properties were first created using three-dimensional printing,[50,63] which couples computer design with polymer fabrication, expelling liquid polymer onto dry, powdered polymer through a machine analogous to an ink-jet printer. As the layers of solidified polymer are built up, complex three-dimensional structures can be formed with high resolution. Therefore, channels for blood supply and cellular support can be designed and fabricated.

FUTURE DIRECTIONS: BETTER STRUCTURES, BETTER CELLS

With the advent of microelectrical mechanical systems (MEMS), also used in inertial guidance and navigation,[9] silicon micromachining has been used to form an improved scaffold for vascular networks. Trench patterns are etched on silicon and Pyrex templates with resolution to 10 μm in patterns that replicate a vascular network (Fig. 3-5). Endothelial cells and hepatocytes cultured on the MEMS template remain viable and proliferative, producing albumin.[9] The monolayers can then be lifted and formed into a three-dimensional structure. Stacking these layers could incorporate a biliary system and increase the available surface area of any vascularized tissue and its parenchyma added to the system.

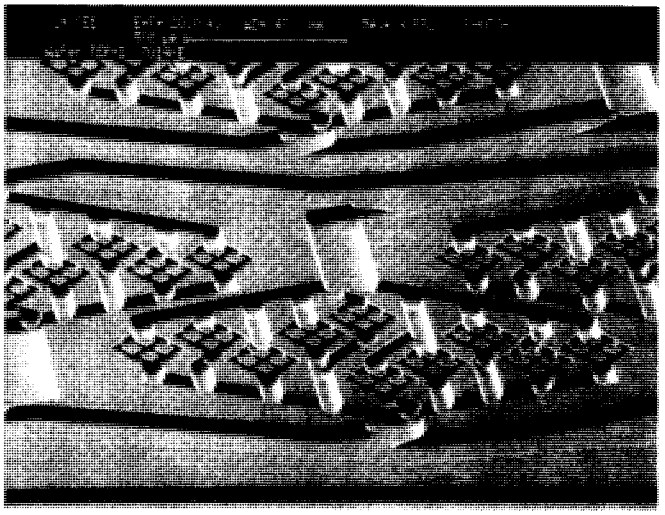


Figure 3–5 Optical micrograph of a portion of a capillary network etched into a silicon wafer using a microelectrical mechanical system. (Courtesy of Dr. J. Borenstein.)

Further studies have confirmed that microfabrication technology can be used to form large sheets of living tissue and that micromachining luminal surfaces for endothelial cells allows ordered co-culture (Fig. 3-6).[9] The lifted organized layers have been implanted as a permanent graft.

Coupled with these advances is the search for a more appropriate cellular population, which may include a mixed culture on a novel scaffold. Improved micromachined templates are already being made in collaboration with Draper Laboratories at the Massachusetts Institute of Technology, with mathematical modeling of the expected microfluidics and nutritional transfer. With the solution to the problem of vascularizing complex organs,

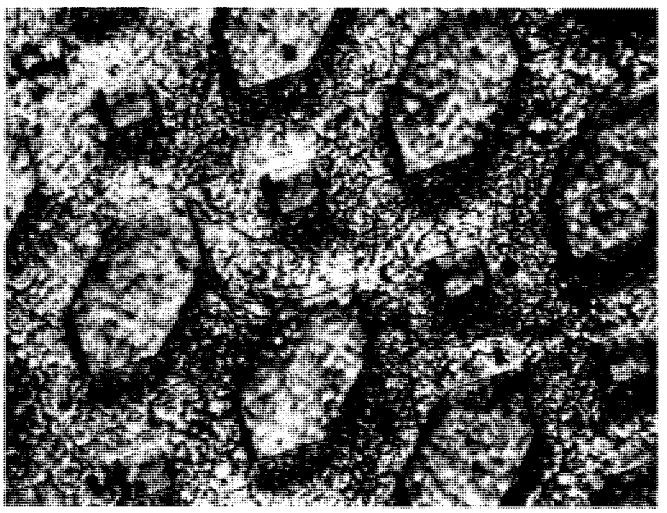


Figure 3–6 Endothelial cells grown on Vitrogen-coated (30 μg/mL) Pyrex wafers after 4 days in culture. (From Kaihara S, Borenstein J, Koka R, et al: Silicon micromachining to tissue engineer branched vascular channels for liver fabrication. Tissue Eng 2000;6:105-117.)

many difficult tissue-engineering targets could finally be within reach.

An evident extension of the tissue-engineering armamentarium is the future use of stem cells or pluripotent cell lines, which involves ethical and political issues that must be addressed. Of note, the majority of tissue-engineering solutions revolve around autologous or syngeneic cells rather than direct stem cell application. The number of projects employing mesenchymal stem cells has rapidly increased, and some in the field have pursued amniotic fluid as a source of mesenchymal stem cells for fetal tissue engineering.[47] In addition, fetal tissues, including chondrocytes for chest wall reconstruction, have been harvested from the lamb fetus, expanded in the laboratory until the birth of the animal, and then implanted at that time, with structural replacement noted up to 10 weeks after implantation.[23] Most tissue-engineering strategies that rely on non–stem cell–based approaches likely make use of the progenitors found in the tissues used, so stem cells have been used in tissue engineering without being clearly identified. It is interesting to note that these cells, already somewhat differentiated, are adequate for the production of many tissues.

The rapid metamorphosis of tissue engineering has occurred primarily through creative collaboration among engineers, chemists, surgeons, physicists, biologists, and scientists in a number of other disciplines, with true progress being made through simultaneous advances in materials, cellular physiology, and surgical application. The evolution of bioreactor devices, including those that stress the cells to approximate physiologic conditions, has also led to better tissues. The combination of mechanical engineering, tissue engineering, and surgical research represents the future of tissue engineering for general and pediatric surgical problems.

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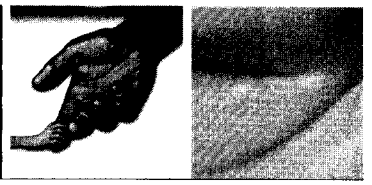
Chapter 4



Advanced and Emerging Surgical Technologies and the Process of Innovation

Russell K. Woo and Thomas M. Krummel

"Change is inevitable. Change is constant" (Benjamin Disraeli). From the eons of evolutionary change that gifted *Homo sapiens* with an opposable thumb, to the minute-to-minute changes of the neonatal surgical patient, change and the adaptive response to change define either success or failure.

The development and use of tools and technologies remain a distinguishing characteristic of the human race. The first hunter-gatherers created, built, and modified tools to the demands of a specific task. In much the same fashion, the relentless development and use of surgical tools and technologies have defined both our craft and our care since the first bone needles were used in prehistoric times.

This chapter endeavors to highlight the advanced and emerging surgical technologies that shape the present and direct future changes. A framework to facilitate both thought and action about the innovations to come is presented. Finally, the surgeon's role in the ethical process of innovation is discussed.

As advances in surgical technologies have occurred, our field has moved forward, often in quantum leaps. A thoughtful look around our operating rooms, interventional suites, critical care units, and even teaching facilities is cause to reflect on our use and even dependence on tools and technologies. Clamps, catheters, retractors, energy sources, and monitors fill these spaces and facilitate and enhance surgeons' capabilities in the process of diagnosis, imaging, physiologic care, molecular triage, and performance of surgical procedures. Surgeons constantly function as users of technology; thus, a fundamental understanding underpins its thoughtful use. Administration of a drug without understanding the mechanism and side effects would be regarded as malpractice. A similar case must be made for the use of surgical tools and technologies.

New technologies result from an endless cycle through which innovation occurs. Such a cycle may begin with a fundamental research discovery or begin at the bedside with an unsolved patient problem. Frequently, innovation requires a complex interplay of both. Surgeons are uniquely positioned and privileged to contribute to and even define this cycle. A patient with an unsolvable problem is a constant reminder of our responsibility to advance our field. Theodore Kocher's success in thyroid surgery was enabled by his toothed modification of existing clamps to facilitate thyroid operations. Dr. Thomas Fogarty's development of the balloon catheter began as a surgical assistant while witnessing both the failures and disastrous consequences of extensive arteriotomies for extraction of emboli. His simple, brilliant concept has arguably created the entire field of catheter-based manipulation. Dr. John Gibbon's successful construction of a heart-lung machine was initially motivated by a patient with an unsolved problem of pulmonary emboli and the need for surgical extraction. Although his original intention has been eclipsed by Lazar Greenfield's suction embolectomy catheter and venacaval filter and dwarfed by the utility of the heart-lung machine in cardiac surgery, the story remains the same. Unresolved problems and a surgeon determined to find a solution have led to countless innovations that have changed our field forever. The surgeon's role must extend outside the operating room. Surgeons must remain aware and connected to the tools and techniques of diagnosis, monitoring, and education. Mark M. Ravitch, extraordinary pediatric surgeon, innovator, and one of the most literate surgeons of the 20th century, described surgery as an intellectual discipline characterized by operative procedures but, most important, defined as an attitude or responsibility toward care of the sick. Dr. Ravitch's contribution to the development of stapling devices deserves enormous credit.[203]

A surgical operation can be defined as "an act performed with instruments or by the hands of a surgeon." This definition implies an image and a manipulation; the manipulation implies an energy source. Historically we

TABLE 4-1 Surgical Operation—Image and Manipulation

Image	Manipulation
Direct visual	2 hands direct
Video image	2 hands, long tools
	Robots
Ultrasound	Cold, thermal
Computed tomography	Radiofrequency
Magnetic resonance imaging	Photodynamic energy
	Focused ultrasound energy

have regarded the "image" to be that of a direct visual image and the "manipulation" to be performed with the direct contact of two hands or surgical tools. The laparoscopic revolution has taught us that the image can be a video image and the manipulation can be performed by two hands with long tools. Now these long tools are occasionally attached to surgical robots. Our notion about the image has come to include ultrasound (US), computed tomography (CT), and magnetic resonance imaging (MRI), and the manipulation can include such sources as cold, heat, radiofrequency (RF), and photodynamic or chemical energy. Extracorporeal shock wave lithotripsy is an important urologic example of this principle applied to renal calculi. How will the "image" and "manipulation" exist in the future (Table 4-1)?

DIAGNOSTIC TECHNOLOGIES

Accurate evaluation of surgical disease has always been a vital aspect of surgical practice and always precedes surgery. Whether in the clinic, in the emergency department, or at the bedside, precise assessment defines surgical judgment and care. A thorough history and detailed physical examination will forever remain the foundation of assessment; however, the thoughtful addition of adjunctive imaging studies has considerably enhanced the evaluation of surgical patients. Driven by advancements in medicine, engineering, and biology, these studies entail increasingly sophisticated technologies that may provide more detailed anatomic, functional, and even molecular information in the future.

Over the past 3 decades, the introduction and improvement of US, CT, and MRI techniques have revolutionized the clinical evaluation of surgical disease. The fine anatomic data provided have facilitated the accurate diagnosis of a wide variety of conditions. Functional imaging techniques, such as positron emission tomography (PET) and functional MRI (fMRI), have been developed to provide accurate and often real-time biologic or physiologic information. In the field of pediatric surgery, these imaging modalities may be used in the diagnosis of disease, for preoperative surgical planning, and for postoperative evaluation. This section provides an overview of the imaging modalities used in pediatric surgery, with a focus on emerging techniques and systems.

Ultrasound

US imaging has become a truly invaluable tool in the evaluation of pediatric surgical patients. Providing anatomic as well as real-time functional information, US has unique attributes that have made it particularly useful, including relatively low cost, portability, flexibility, and safety inasmuch as no ionizing radiation is used. For these reasons, this section will focus on US imaging and highlight emerging advances in its technology and practice, including three-dimensional (3-D) US imaging, US contrast imaging, and US harmonic imaging.

US uses the emission and reflection of sound waves to construct images of body structures. It operates on the same principle as active SONAR—a sound beam is projected by the US probe into the body, and based on the time to "hear" the echo, the distance to a target structure can be calculated.[123] In the body, sound waves are primarily reflected at tissue interfaces, with the strength of the returning echoes mainly correlating with tissue properties. Advantages of US imaging include lack of ionizing radiation, real-time imaging with motion, and relatively fast procedure times.[213]

In modern US devices, numerous transducer elements are placed side by side in the transducer probe. The majority of devices currently use linear or sector scan transducers. These transducers consist of 64 to 256 piezoelectric elements arranged in a single row that allow the transducer to interrogate a single slice of tissue whose thickness is correlated to the thickness of the transducer elements.[123] This information is then used to construct real-time, dynamic, two-dimensional (2-D) images. Color, power, and pulsed wave Doppler imaging techniques are enhancements of this technology that allow color or graphic visualization of motion.[213] Conventional Doppler imaging provides information on flow velocity and direction of flow by tracking scattering objects in a region of interest.[61] In contrast, power Doppler displays the power of the Doppler signal and is a more sensitive method in terms of signal-to-noise ratio and low-flow detection.[172]

In pediatric surgery, US imaging is widely used in the evaluation of appendicitis, testicular torsion, intussusception, hypertrophic pyloric stenosis, biliary and pancreatic conditions, and pelvic pathology.[54,74] In addition, US is a powerful and relatively safe tool for the prenatal diagnosis of congenital anomalies such as abdominal wall defects, diaphragmatic hernia, sacrococcygeal teratoma, cystic adenomatoid malformation, pulmonary sequestration, neural tube defects, obstructive uropathy, facial clefting, and twin-twin syndrome.[163] Sonographic guidance is also vital in performing more invasive prenatal diagnostic techniques such as amniocentesis and fetal blood sampling.[163]

Ultrasound and Fetal Surgery

Prenatal US provided the first view of the developing fetus, helped define the natural history of the fetus with an anomaly, and suggested prenatal interventional strategies.[85] US evaluation has become an increasingly important noninvasive modality for diagnosing and characterizing diseases

that are amenable to fetal surgical intervention.[237] Today, fetal surgical techniques are used in selected centers to perform a variety of procedures, including surgical repair of myelomeningocele, resection of sacrococcygeal teratoma in fetuses with nonimmune hydrops, resection of an enlarging congenital cystic adenomatoid malformation that is not amenable to thoracoamniotic shunting, and tracheal clip occlusion for severe left congenital diaphragmatic hernia.[42,45] Sonography currently remains the modality of choice for fetal diagnosis and treatment because of its safety and real-time capabilities. In addition, US imaging is vital to the postoperative care and follow-up of fetal surgical patients in utero.

Three-Dimensional Ultrasound

Although 2-D ultrasound systems have improved dramatically over the past 30 years, 2-D images require experienced interpretation. These images represent one cross section, or slice, of the target anatomy and thus require interpretation to mentally reconstruct the 3-D picture. Given these limitations, 3-D US systems that provide volumetric instead of cross-sectional images have recently been developed and have seen increased use for many applications.

The first reported clinical use of a 3-D US system occurred in 1986 when Baba succeeded in obtaining 3-D fetal images by processing 2-D images on a minicomputer (*http://www.ob-ultrasound.net/history-3D.html*). Since then, multiple 3-D US systems have been developed to provide more detailed and cohesive anatomic information. These multislice or volumetric images are generally acquired by one of two techniques: (1) utilization of a 2-D array in which a transducer with multiple element rows is used to capture multiple slices at once and render a volume from real 3-D data and (2) utilization of a one-dimensional phased array to acquire several 2-D slices over time. The resultant images are then fused by the US computer's reconstruction algorithm.

The 3-D information acquired via these techniques is then used to reconstruct and display a 3-D image by maximal signal intensity processing, volume rendering, or surface rendering. When these 3-D images are displayed in real-time fashion, they have the ability to provide both anatomic and functional information. An example is the evaluation of cardiac function with real-time US. Real-time, 3-D US is sometimes referred to as four-dimensional US (including the dimension of time), although it is still essentially providing a 3-D image. A 3-D US view of a fetus in utero is presented in Figure 4-1.

In the field of pediatric and fetal surgery, these 3-D US systems have been used for detailed prenatal evaluation of congenital anomalies. Dyson et al. prospectively scanned 63 patients with 103 anomalies via both 2-D and 3-D US techniques. Each anomaly was reviewed to determine whether 3-D US data were either advantageous, equivalent, or disadvantageous when compared with 2-D US images. The 3-D US images provided additional information in 51% of the anomalies, provided equivalent information in 45% of the anomalies, and were disadvantageous in 4%. Specifically, 3-D US techniques were most helpful in evaluating fetuses with facial anomalies, hand and foot abnormalities, and axial spine and neural tube defects. Overall, 3-D US imaging offered diagnostic advantages in about half the selected cases studied and had a significant effect on patient management in 5% of cases. They concluded that 3-D US was a powerful adjunctive tool to 2-D US in the prenatal evaluation of congenital anomalies.[52]

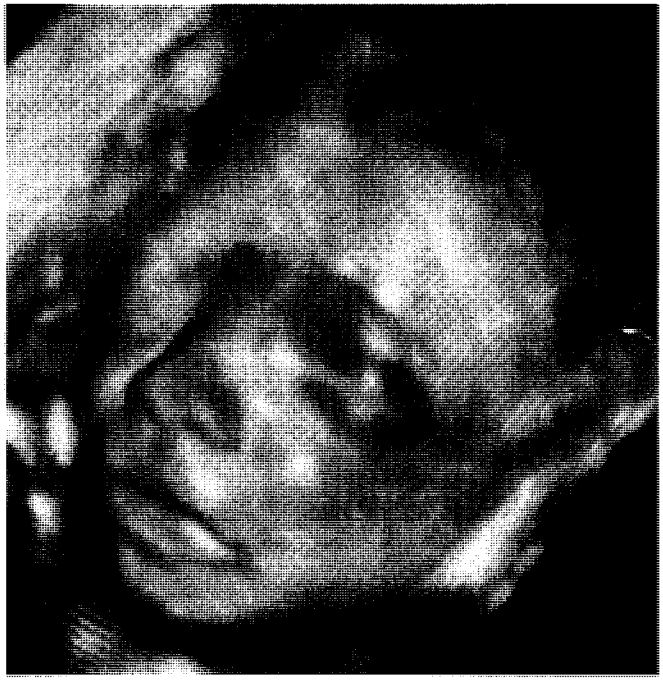


Figure 4–1 Three-dimensional ultrasound image of a fetal face. (From Tonni G, Centini G, Rosignoli L: Prenatal screening for fetal face and clefting in a prospective study on low-risk population: Can 3- and 4-dimensional ultrasound enhance visualization and detection rate? Oral Surg, Oral Med Oral Pathol Oral Radiol Endod 2005;100:420.

Chang et al. reported several series in which 3-D US techniques were used to effectively evaluate fetal organ volumes. They used 3-D US to accurately estimate fetal lung volume for the evaluation of pulmonary hypoplasia,[30] cerebellar volume,[27,28] heart volume,[31] adrenal gland volume,[29] and liver volume.[32] In all these studies, 3-D US images provided more accurate data than 2-D images did.[32]

In addition to prenatal evaluation, 3-D US systems have been used to image the ventricular system in neonates and infants to aid in the preoperative planning of neuroendoscopic interventions.[104,105] Similarly, these systems have seen relatively extensive use in the area of transthoracic echocardiographic imaging for the evaluation of congenital cardiac anomalies.[122,137] Cannon et al. studied the ability of 3-D US to guide basic surgical tasks in a simulated endoscopic environment.[25] They found that 3-D US imaging guided these tasks more efficiently and more accurately than 2-D US imaging did.[25] 3-D US systems allow the visualization of complex structures in a more intuitive manner than possible with 2-D systems. In addition, they appear to enable more precise measurements of volume and the relative orientation of structures.[222] As technology improves, the use of such systems in the field of pediatric surgery is likely to increase.

Ultrasound Contrast Imaging and Ultrasound Harmonic Imaging

In addition to 3-D US, significant advancements have occurred in US contrast imaging and harmonic imaging. US contrast imaging techniques are currently used for the visualization of intracardiac blood flow in order to evaluate structural anomalies of the heart.[225] US contrast agents are classified as free gas bubbles or encapsulated gas bubbles. These gas bubbles exhibit a unique resonance phenomenon when isonified by a US wave. They exhibit a frequency-dependent volume pulsation that makes the resonating bubble behave as a source of sound, not just a reflector of it.[61] New methods are being developed to enhance the contrast effect, including harmonic imaging, harmonic power Doppler imaging, pulse inversion imaging, release-burst imaging, and subharmonic imaging.[61] As these methods improve, US contrast imaging may provide clinicians with more detailed perfusion imaging of the heart, as well as tumors, arteriovenous malformations, and other conditions. Figure 4-2 depicts a US image of the left ventricle with the use of microbubble contrast.

Interest in US harmonic imaging occurred in 1996 after Burns observed harmonics generated by US contrast agents.[21] Since then, significant development has occurred in utilization of the harmonic properties of sound waves to improve the quality of US images. Sound waves are the sum of different component frequencies—the fundamental frequency (first harmonic) and harmonics, which are integral multiples of the fundamental frequency. The combination of the fundamental frequency and its specific harmonics gives a signal its unique characteristics. Harmonics are generated by the tissue itself; when US contrast agents are used, harmonics are generated by reflections from the injected agent and not by reflections from tissue.[221]

Whereas the fundamental frequency consists of echoes produced by tissue interfaces and differences in tissue properties, the harmonics are generated by the tissue itself. In this manner, harmonic intensity increases with depth up to the point at which natural tissue attenuation overcomes this effect. In contrast, the intensity of the fundamental frequency is attenuated linearly with depth.[221]

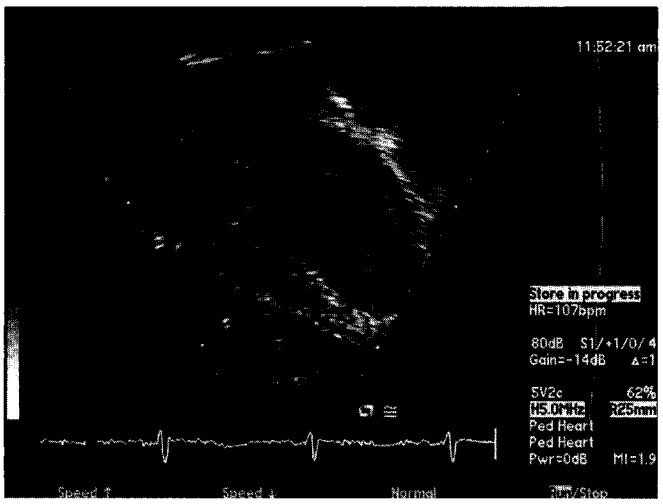


Figure 4–2 Ultrasound contrast echocardiogram demonstrating microbubbles in the right heart. (Courtesy of the Lucille Packard Children's Hospital Echocardiography Laboratory.)

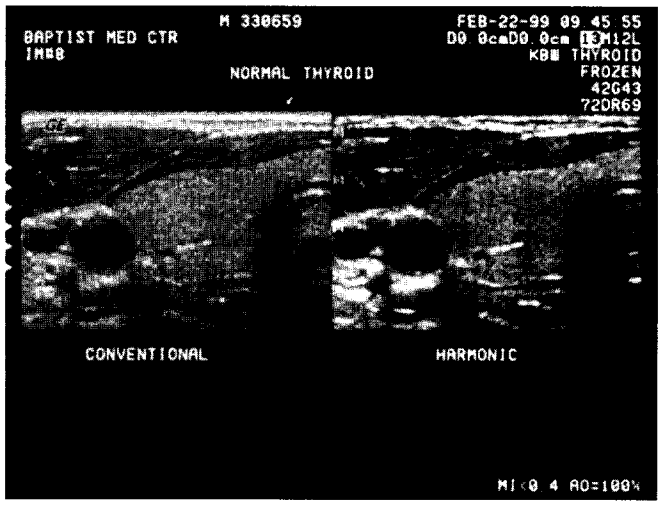


Figure 4–3 Conventional versus ultrasound harmonic imaging.

Tissue harmonic imaging takes advantage of these properties by using the harmonic signals that are generated by tissue and filtering out the fundamental echo signals that are generated by the transmitted acoustic energy.[60] Such filtering theoretically leads to an improved signal-to-noise ratio and contrast-to-noise ratio. Additional benefits of US harmonic imaging include improved spatial resolution, better visualization of deep structures, and a reduction in artifacts produced by US contrast agents.[29] Figure 4-3 compares an image obtained by US harmonic imaging and one obtained by standard 2-D US.

Computed Tomography

CT was invented in 1972 by British engineer Godfrey Hounsfield of EMI Laboratories, England, and independently by the South African–born physicist Allan Cormack of Tufts University, Massachusetts. Since then, the medical use of CT imaging has become widespread. Currently, advances in technology have improved the speed, comfort, and image quality. Recent advances such as multidetector CT (MDCT) and volumetric reconstruction, or 3-D CT, may be particularly valuable in the care of pediatric surgical patients. This section provides a brief overview of CT imaging with focus on MDCT and volumetric imaging and their implications in pediatric surgery.

Multidetector Computed Tomography

CT uses a tightly arranged strip of radiation emitters and detectors circled around a patient to obtain a 2-D map of x-ray attenuation values. Numerical regression techniques are then used to turn this list of attenuation values into a 2-D slice image. CT has undergone several major developments since its introduction.

Introduced in the early 1990s, single-detector helical or spiral CT scanning revolutionized diagnostic CT imaging by

using slip rings to allow for continuous image acquisition.[127] Before this development, the table and patient were moved in stepwise fashion after the acquisition of each image slice, a process that resulted in relatively long scanning times. Helical CT scanners use slip ring technology that allows the tube and detector to continually rotate around the patient. When combined with continuous table motion through the rotating gantry, speed is significantly improved. The improved speed of helical CT scanners enabled the acquisition of large volumes of data in a single breath hold, which has facilitated widespread pediatric use.

Helical CT has improved over the past 8 years, with faster gantry rotation, more powerful x-ray tubes, and improved interpolation algorithms.[183] However, the greatest advance has been the recent introduction of MDCT scanners. In contrast to single–detector row CT, MDCT uses multiple parallel rows of detectors that spiral around the patient simultaneously. Currently capable of acquiring four channels of helical data at the same time, MDCT scanners are significantly faster than single-detector helical CT scanners. This has profound implications on the clinical application of CT imaging, especially in pediatric patients, where the issues of radiation exposure and patient cooperation are magnified. Fundamental advantages of MDCT in comparison to earlier modalities include substantially shorter acquisition times, retrospective creation of thinner or thicker sections from the same raw data, and improved 3-D rendering with diminished helical artifacts.[183]

In the pediatric population, MDCT provides a number of advantages over standard helical CT, including a shortened or decreased need for sedation, a reduction in patient movement artifact, and a potential for more optimal contrast enhancement over a greater portion of the anatomic site. The volumetric data acquired also provide for the ability to perform multiplanar reconstruction, which can be an important problem-solving tool. MDCT has increasingly been used for pediatric trauma, pediatric tumors, evaluation of solid abdominal parenchymal organ masses, suspected abscess or inflammatory disorders,[63] and evaluation of abdominal pain.[49] Callahan et al. used MDCT to evaluate children with appendicitis and reduced the total number of hospital days, negative laparotomy rate, and cost per patient.[24] In addition, MDCT may be useful in identifying alternative diagnoses of pediatric abdominal pain, including bowel, ovarian, and urinary tract pathologies[49] (Fig. 4-4).

Similarly, MDCT may be valuable in the evaluation of urolithiasis and inflammatory bowel disease (IBD). MDCT has gained acceptance as a primary modality for the evaluation of children with abdominal pain and hematuria in whom urolithiasis is suspected.[49] CT findings of urolithiasis include visualization of radiopaque stones, dilatation of the ureter or collecting system, asymmetric enlargement of the kidney, and perinephric stranding.[49] Another condition in which CT is increasingly being used is IBD in children.[49] In the evaluation of these patients, CT may be superior to fluoroscopy in demonstrating inflammatory changes within the bowel, as well as extraluminal manifestations of IBD such as abscess.[49]

In the chest, MDCT has been used in children with infections, for detection and surveillance, and for evaluation of congenital abnormalities of the lung, mediastinum, and heart. In particular, MDCT may be useful in the assessment of bronchopulmonary foregut malformation in which sequestration is a consideration.[62] The use of MDCT has been particularly valuable for evaluation of the pediatric cardiovascular system.[47] Assessment of cardiovascular conditions such as aortic aneurysms, dissections, and vascular rings may be significantly better than with echocardiography. Finally, MDCT is advantageous in the quantitative evaluation of patients with chest wall deformities because it allows for lower doses of radiation.[49]

Figure 4-4 Multidetector computed tomogram of an 8-year-old boy with appendicitis. The *arrows* point to an inflammatory mass in the right lower quadrant with a possible appendicolith (*arrowhead*).

Three-Dimensional Computed Tomography

Postacquisition processing of individual studies for the creation of 3-D CT reconstructions has been enabled by MDCT. These 3-D reconstructions are of value in the preoperative planning for complex surgical procedures. Although 3-D CT has been available for almost 20 years, the quality, speed, and affordability of these techniques have only recently improved enough to result in their incorporation in routine clinical practice.[100] Currently, four main visualization techniques are used in CT reconstruction laboratories to create 3-D CT images: multiplanar reformation, maximum intensity projections, shaded surface displays, and volume rendering. Multiplanar reformation and maximum intensity projections are limited to external visualization, whereas shaded surface displays and volume rendering allow for immersive or internal visualization such as virtual endoscopy.[183]

3-D CT is beneficial in the preoperative planning of pediatric craniofacial, vascular, and spinal operations. Specifically, 3-D CT is used to evaluate maxillofacial fractures,[58] craniofacial abnormalities (Fig. 4-5), and vascular malformations. 3-D CT has been useful in the planning of hemivertebra excision procedures for thoracic and thoracolumbar congenital deformities.[87]

A particularly interesting application of 3-D CT is the creation of "virtual endoscopy" images. The interior surface of luminal structures such as the bowel, airways, blood vessels, and urinary tract is reconstructed.[183] Virtual endoscopy using 3-D CT may be useful in the

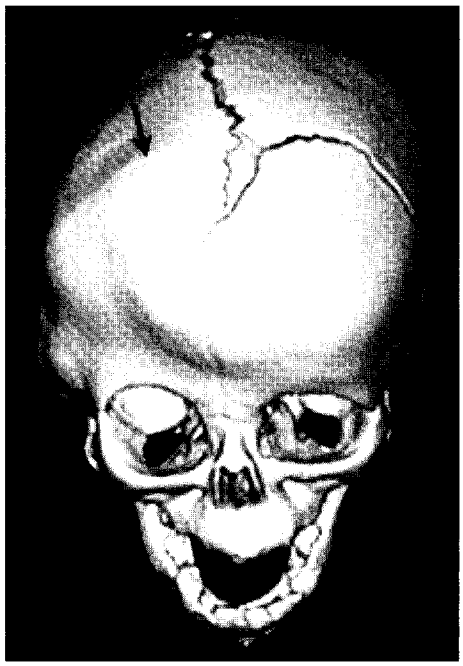


Figure 4–5 Three-dimensional computed tomographic T reconstruction of an infant skull showing premature closure of the right coronal suture (*arrow*).

diagnosis of small bowel tumors, lesions that are often difficult to detect with standard modalities[100] (Fig. 4-6).

Magnetic Resonance Imaging

The first MRI examination on a human was performed in 1977 by Drs. Damadian, Minkoff, and Goldsmith. This initial examination took 5 hours to produce one relatively poor-quality image. Since then, technologic enhancements have improved the resolution and speed of MRI. Today, MRI is able to provide unparalleled noninvasive images of the human body. Newer MRI systems currently allow images to be obtained at subsecond intervals, thereby facilitating fast, near real-time MRI. MRI techniques are now being developed to provide functional information on the physiologic state of the body. This section provides a brief overview of MRI with a focus on recent technologic advances such as ultrafast MRI and fMRI.

MRI creates images by using a strong uniform magnetic field to align the spinning hydrogen protons of the human body. An RF pulse is then applied and causes some of the protons to absorb the energy and spin in a different direction. When the RF pulse is turned off, the protons realign and release their stored energy. This release of energy gives off a signal that is detected, quantified, and sent to a computer. Because different tissues respond to the magnetic field and RF pulse in a different manner, they give off variable energy signals. These signals are then used to create an image via mathematical algorithms.

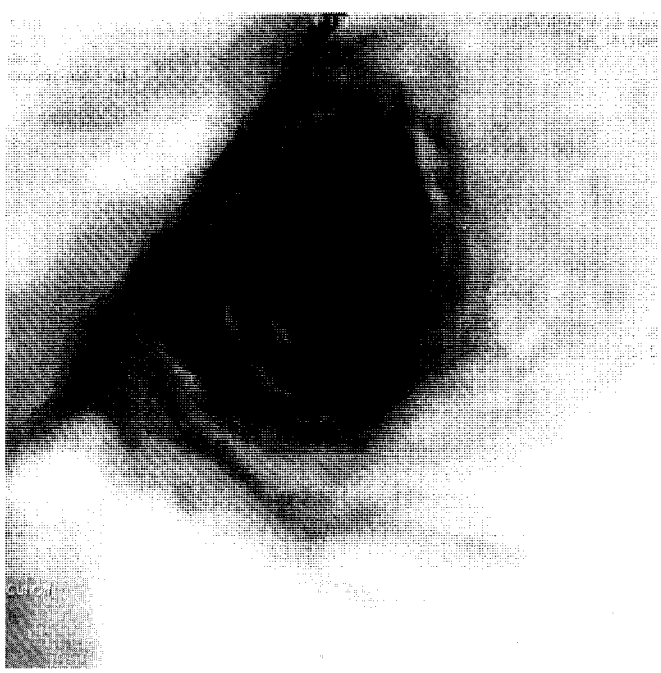


Figure 4–6 Virtual endoscopy.

Ultrafast MRI

The first major development in high-speed MRI occurred in 1986 with introduction of the gradient-echo pulse sequence technique (GRE), which can decrease practical scan times to as short as 10 seconds. In addition to increasing the patient throughput of MRI scanners, the faster scan times significantly increased the application of MRI to body regions (e.g., the abdomen) where suspended respiration could eliminate most motion-related image distortions.[53,226] Since then, GRE techniques have undergone iterations and further developments, and subsecond scan times have been achieved. Currently, ultrafast MRI sequences are able to obtain high-resolution scans in times as fast as one tenth of a second. These ultrafast MRI techniques have revolutionized the practical application of MRI in clinical medicine by reducing motion artifact. It has enabled newer, dynamic imaging modalities, including cardiac MRI, fetal MRI, and physiologic imaging techniques such as diffusion perfusion scanning (potentially valuable in the assessment of cerebral viability during stroke) and fMRI.

Ultrafast MRI provides a significant advantage in the care of children. Most traditional MRI protocols require 30 to 40 minutes, during which the patient must remain still.[199] For many children, sedation, general anesthesia, and even muscular blockade are often required to enable them to remain motionless long enough for a study to be completed. These were major impediments in performing MRI in children. Ultrafast MRI significantly reduces this requirement, thereby not only minimizing the potential side effects of sedation during routine MRI studies but also allowing the use of MRI to study high-risk infants who cannot be adequately sedated or paralyzed.[243]

In addition, ultrafast MRI significantly reduces the motion artifacts that occur in the abdomen and thorax as a result of normal respiratory and peristaltic movements. This is accomplished by achieving scan times that are rapid enough to be completed during a breath hold and

fast relative to normal abdominal motion. Ultrafast MRI has been particularly useful in decreasing the smearing artifact associated with the use of oral contrast agents during MRI of the intestinal tract.[81] Moreover, by decreasing motion artifact and enabling fast image acquisition, ultrafast MRI protocols have enabled the practical application of cardiac MRI and fetal MRI. Fetal MRI is currently being used to better identify and characterize fetal brain and spine abnormalities.[73,174]

Functional MRI

fMRI is a rapidly evolving imaging technique that uses blood flow differences in the brain to provide in vivo images of neuronal activity. First described just over 10 years ago, fMRI has seen widespread clinical and research application in the adult population. fMRI is founded on two basic physiologic assumptions regarding neuronal activity and metabolism. Specifically, it assumes that neuronal activation induces an increase in local glucose metabolism associated with an increase in local cerebral blood flow. By detecting small changes in local blood flow, fMRI techniques are able to provide a "functional" image of brain activity. Currently, the most commonly used technique is known as "blood oxygen level–dependent" (BOLD) contrast, which uses blood as an internal contrast medium.[48] BOLD imaging takes advantage of small differences in the magnetic properties of oxygenated and deoxygenated hemoglobin. Because neuronal activation is followed by increased and relatively excessive local cerebral blood flow, more oxygenated hemoglobin appears in the venous capillaries of activated regions of the brain. These differences are detected as minute distortions in the magnetic field by fMRI and can be used to create a functional image of brain activity.[236]

In the pediatric population, fMRI requires significant subject preparation to have the child remain still in the scanner for the duration of the study. Various preparation techniques have been described for decreasing the anxiety and uncertainty that a child might experience regarding the study, including presession educational videos, tours with members of the radiology staff, and practice runs. Unlike anatomic MRI, patients undergoing fMRI cannot be sedated or anesthetized because this influences neuronal activity.

At this time, the use of fMRI in the pediatric population is still in its earliest stages. However, fMRI holds tremendous promise in the evaluation of central nervous system organization and development, characterization of brain plasticity, and evaluation and understanding of neurobehavioral disorders.[236] In addition, current clinical applications of fMRI include the delineation of eloquent cortex near a space-occupying lesion and determination of the dominant hemisphere for language. These clinical applications are designed to provide preoperative functional information before a planned neurosurgical procedure.[236]

Positron Emission Tomography

PET is an increasingly used imaging technology that provides information on the functional status of the human body. First developed in 1973 by Hoffman, Ter-Pogossian, and Phelps at Washington University, PET is now one of the most commonly performed nuclear medicine studies.[94] Although CT, MRI, and US techniques provide detailed information regarding the patient's anatomy, PET provides information on the current metabolic state of the patient's tissues.[107] In this manner, PET is often able to detect metabolic changes indicative of a pathologic state before anatomic changes can be visualized.

PET imaging is based on the detection of photons released when positron-emitting radionuclides undergo annihilation with electrons.[209] These radionuclides are created by bombarding target material with protons that have been accelerated in a cyclotron.[209] Positron-emitting radionuclides are then used to synthesize radiopharmaceuticals that are part of biochemical pathways in the human body. The most commonly used example is a fluorinated analogue of glucose, 2-deoxy-2-[^{18}F] fluorodeoxyglucose (FDG). Like glucose, FDG is phosphorylated by the intracellular enzyme hexokinase.[219] In its phosphorylated form, FDG does not cross cell membranes and therefore accumulates within metabolically active cells. In this manner, PET imaging with FDG provides information on the glucose utilization of different body tissues.[107,219]

To be detected, FDG is synthesized with ^{18}F, a radioisotope with a half-life of 110 minutes. The synthesis process begins by accelerating negatively charged hydrogen ions in a cyclotron until they gain approximately 8 MeV of energy. The orbital electrons from these hydrogen ions are then removed by passing them through a carbon foil. The resultant high-energy protons are next directed toward a target chamber that contains stable ^{18}O-enriched water. The protons undergo a nuclear reaction with the ^{18}O-enriched water to form hydrogen ^{18}F-fluoride. The reaction is detailed in the following equation[107]:

$$H_2(^{18}O) + {}^{1}H + \text{Energy} \rightarrow H_2(^{18}F)$$

^{18}F is an unstable radioisotope that decays by β^+ emission or electron capture and emits a neutrino (ν) and a positron (β^+). The emitted positrons are then annihilated with electrons to release energy in the form of photons, which are detected by modern PET scanners. The detectors in PET scanners are scintillation crystals coupled to photomultiplier tubes. Currently, most PET scanners use crystals composed of bismuth germinate, cerium-doped lutetium oxyorthosilicate, or cerium-doped gadolinium silicate. Because PET scanning uses unstable radioisotopes, PET probes must be synthesized immediately before a PET study. This drawback limits the immediate and widespread availability of PET imaging because the studies must therefore be scheduled in advance. FDG is a convenient probe because its half-life of 110 minutes allows it to be transported from a remote cyclotron to a PET scanner in enough time to perform a typical whole-body PET imaging study (≥30 minutes).

In a typical PET study, the radiopharmaceutical agent is administered intravenously. The patient is imaged by the PET scanner, which measures the radioactivity (photon emission as previously described) throughout the body and creates 3-D pictures or images of tissue function. Currently, PET imaging is used extensively in the evaluation and monitoring of tumors of the lung, colon, breast,

lymph nodes, and skin.[193] PET imaging has been used to facilitate tumor diagnosis, localization, and staging, monitoring of antitumor therapy, tumor tissue characterization, radionuclide therapy, and screening for tumor recurrence.[202,212] Though nonspecific, FDG is often used because malignant cells generally display increased glucose utilization with up-regulation of hexokinase activity.

PET imaging has also been used to assess the activity of noncancerous tissues to provide information regarding their viability or metabolic activity. In adults, PET scans are often used to determine the viability of cardiac tissue to decide whether a patient would benefit from coronary bypass grafting.[75,76] Recently, this application has been extended to the pediatric population to assess cardiac function after arterial switch operations with suspected myocardial infarction.[177] Similarly, PET scans can visualize viability of brain tissue to make prognostic determinations after stroke.[173] Finally, PET imaging has been used to identify regions of abnormal activity in brain tissue and as such can help localize seizure foci or diagnose functional disorders such as Parkinson's disease and Alzheimer's disease.[157,158]

Although PET imaging provides important functional information regarding the metabolic activity of human tissues, it often provides relatively imprecise images when compared with traditional anatomic imaging modalities. It may be difficult to use during preoperative planning because it does not accurately correlate the area of suspicion with detailed anatomic information. Recently, combined PET/CT scanners have been developed that simultaneously perform PET scans and high-resolution CT scans.[192] Introduced only 5 years ago, these scanners provide functional information obtained from the PET scan and accurately map it to the fine anatomic detail of the CT scan[220] (Fig. 4-7).

In the field of pediatric surgery, PET/CT scanning represents a new imaging modality with tremendous potential in regard to preoperative planning and postoperative follow-up. However, several issues specific to the pediatric population make the implementation of PET imaging challenging, including the need for fasting, intravenous access, bladder catheterization, sedation, and clearance from the urinary tract.[109,180] Currently, the clinical application of combined PET/CT imaging in children has not been extensively studied. However, the combination of functional information with fine anatomic data provides obvious advantages with respect to surgical planning and will probably play a larger role in surgical practice in the future.

Molecular Imaging

US, CT, MRI, and PET are established technologies that are commonly used in the care of pediatric patients. Although these technologies provide detailed anatomic and even functional information, their clinical application has yet to provide information at the cellular/molecular level. In contrast to these classic imaging modalities, a new field termed "molecular imaging" probes the molecular abnormalities that are the basis of disease rather than imaging the end effects of these alterations. Molecular imaging is a rapidly growing research discipline that combines molecular and cell biology with noninvasive imaging technologies.[233] The goal of this new field is to develop techniques and assays for imaging physiologic events and pathways in living organisms at the cellular/molecular level, particularly pathways that are key targets in specific disease processes. The development and application of molecular imaging will someday probably affect patient care by elucidating the molecular processes underlying disease and lead to early detection of molecular changes that represent "predisease" states.[91]

Molecular imaging can be defined as the in vivo characterization and measurement of biologic processes at the cellular and molecular level. From a simplistic standpoint, molecular imaging consists of two basic elements: (1) molecular probes whose concentration, activity, or luminescence (or any combination of these properties) is changed by the specific biologic process under investigation and (2) a means by which to monitor these probes.[15,145] At the current time, most molecular probes are either radioisotopes that emit detectable radioactive signals or light or near-infrared–emitting molecules. In general, probes are considered either direct binding probes or indirect binding probes. Radiolabeled antibodies designed to facilitate the imaging of cell-specific surface antigens or epitopes are commonly used examples of direct binding probes. Similarly, radiolabeled oligonucleotide antisense probes developed to specifically hybridize with target mRNA or proteins for the purpose of direct, in vivo imaging are more recent examples.[38] Radiolabeled oligonucleotides represent complementary sequences to a small segment of target mRNA or DNA and therefore allow direct imaging of endogenous gene expression at the transcriptional level. Finally, positron-emitting analogues of dopamine, used to image the dopamine receptors of the brain, are other types of direct binding probes.

Whereas direct binding probes assist in imaging the amount or concentration of their targets, indirect probes reflect the activities of their macromolecular targets. Perhaps the most widely used example of an indirect binding probe is the hexokinase substrate FDG. The most common probe used in clinical PET imaging, FDG has been used for neurologic, cardiovascular, and oncologic investigations. Systemically administered FDG is accessible to essentially all tissues.

The use of reporter transgene technology is another powerful example of molecular imaging with indirect binding probes. Reporter genes are nucleic acid sequences that encode easily assayed proteins. Such reporter genes have long been used in molecular biology and genetics studies to investigate intracellular properties and events such as promoter function/strength, protein trafficking, and gene delivery. Via molecular imaging techniques, reporter genes have now been used to analyze gene delivery, immune cell therapy, and the in vivo efficacy of inhibitory mRNA in animal models.[191] In vivo bioluminescent imaging using firefly or *Rinella* luciferase and fluorescent optical imaging using green fluorescent protein or DsRed are optical imaging examples of this technique.

In the field of immunology and immunotherapy research, Costa et al. transduced the autoantigen-reactive

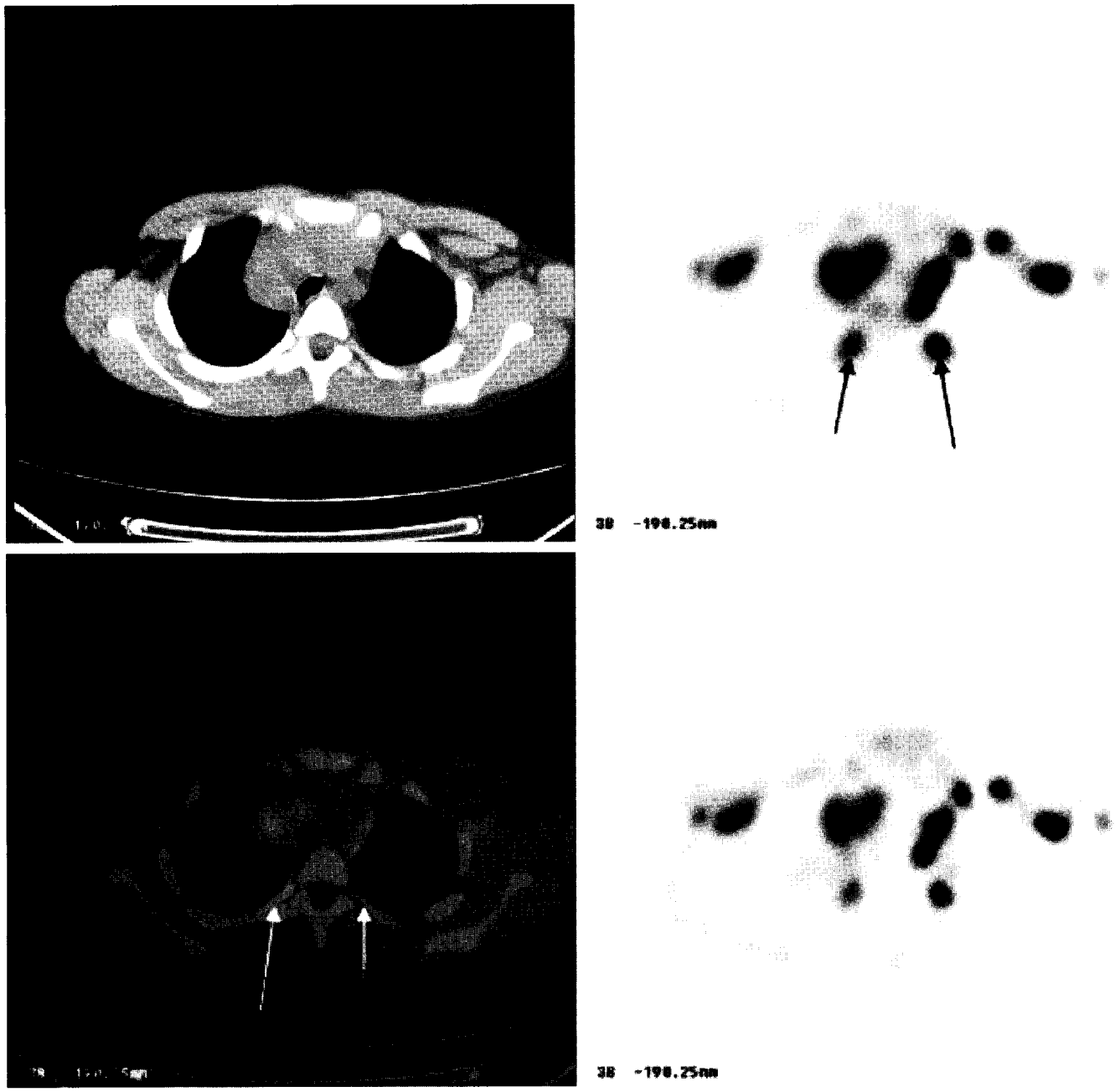


Figure 4–7 Combined PET/CT images (axial) through the upper part of the chest of a 7-year-old girl with necrotizing granuloma. Multiple sites of ^{18}F-FDG avid axillary lymph nodes and multiple foci within the mediastinal mass are visualized. (From Kaste SC: Issues specific to implementing PET-CT for pediatric oncology: What we have learned along the way. Pediatr Radiol 2004;34:205.)

CD4+ T-cell population specific for myelin basic protein with a retrovirus that encoded a dual reporter protein composed of green fluorescent protein and luciferase along with a 40-kDa monomer of interleukin-12 as a therapeutic protein.[44] Bioluminescent imaging techniques were then used to monitor the migratory patterns of the cells in an animal model of multiple sclerosis. Bioluminescent imaging demonstrated that the immune cells that would typically cause destruction of myelin trafficked to the central nervous system in symptomatic animals. Furthermore, they found that CD4+ T-cell expression of the interleukin-12 immune modulator resulted in a clinical reduction in disease severity.[44]

Similarly, Vooijs et al. generated transgenic mice in which activation of luciferase expression was coupled to deletion of the retinoblastoma (*Rb*) tumor suppressor gene.[230] Loss of *Rb* triggered the development of pituitary tumors in their animal model, which allowed them to monitor tumor onset, progression, and response to therapy in individual animals by repeated imaging of luciferase activity with charge-coupled devices.[230] Although optical imaging techniques are commonly used, reporter genes

can also encode for extracellular or intracellular receptors or transporters that bind or transport a radiolabeled or paramagnetic probe, thereby allowing for PET-, single-photon emission computed tomography (SPECT)-, or MRI-based molecular imaging. The second major element of molecular imaging is the imaging modality/technology itself. Direct and indirect binding probes can be radiolabeled to allow for nuclear-based in vivo imaging of a desired cellular/molecular event or process by PET or SPECT imaging. In fact, micro-PET and micro-SPECT systems have been developed specifically for molecular imaging studies in animal models. Similarly, optical imaging techniques such as bioluminescent imaging, near-infrared spectroscopy, visible light imaging with sensitive charge-coupled devices, and intravital imaging can be used with optically active probes to visualize desired cellular events. Finally, anatomic imaging modalities such as MRI, CT, and US have all been adopted for use in animal-based molecular imaging studies.

At this time, the field of molecular imaging is largely experimental, with significant activity in the laboratory and little current clinical application. However, molecular imaging research has been focused on investigating the molecular basis of clinical disease states and their potential treatments. Currently, molecular imaging techniques are being used to investigate the mechanisms surrounding apoptosis, angiogenesis, tumor growth and development, and gene therapy.

DNA Microarrays

The descriptive term *genomics* acknowledges the shift from a desire to understand the actions of single genes and their individual functions to a more integrated understanding of the simultaneous actions of multiple genes and the subsequent effect exerted on cellular behavior. DNA microarrays, or gene chips, are a recent advance that allow for the simultaneous assay of thousands of genes.[17] Microarray technology has been applied to redefine the biologic behavior of tumors, cross-species genomic comparisons, and large-scale analyses of gene expression in a variety of conditions. In essence, it represents a new form of patient and disease triage, *molecular triage.*

THERAPEUTIC TECHNOLOGIES

A surgical operation requires two key elements: an "image" or, more broadly, information regarding the anatomy of interest; and "manipulation" of the patient's tissue to achieve the goal of a therapeutic effect. Classically, the "image" is obtained through the eyes of the surgeon and the "manipulation" is performed with the surgeon's hands and simple, traditional surgical instruments. During the past several decades, this paradigm has been broadened by technologies that enhance these two fundamental elements.

As opposed to standard line-of-sight vision, an "image" may now be obtained through an operating microscope, a flexible endoscope, or a laparoscope. The endoscope may be monocular or binocular to provide 2-D or 3-D visualization. These technologies provide the surgeon with high-quality, magnified images of anatomic areas that may be inaccessible with the naked eye. Similarly, surgical "manipulation" of tissue may be accomplished with a catheter, flexible endoscope, or longer laparoscopic instruments. Furthermore, devices such as staplers, electrocautery, ultrasonic energy tools, and RF emitters are used to manipulate and affect tissue with a therapeutic goal. These technologies have changed the way surgical procedures are performed; they have enabled and even created fields such as laparoscopic surgery, interventional endoscopy, and catheter-based intervention. In addition to these advances, several emerging technology platforms promise to further broaden this definition of surgery, including stereotactic radiosurgery and surgical robotics. This section presents a review of several of these technologies with a focus on the current status of hemostatic and tissue ablative instruments, stereotactic radiosurgery, and surgical robotics.

Hemostatic and Tissue Ablative Instruments

Hand-held energy devices designed to provide hemostasis and ablate tissue are widely used surgical technologies. Since the first reports concerning electrosurgery in the 1920s, multiple devices and forms of energy have been developed to minimize blood loss, including monopolar and bipolar electrocautery, ultrasonic dissectors, argon beam coagulators, cryotherapy, and infrared coagulators. This section provides a broad overview of the various hemostatic and tissue ablative devices with a focus on their principles of operation and techniques of use.

Monopolar Electrocautery

Although the concept of applying an electrical current to living tissue has been reported as far back as the late 16th century, the practical application of electrocautery in surgery did not begin to develop until the early 1900s. In 1908, Lee deForest developed a high-frequency generator that was capable of delivering a controlled cutting current. However, this device used expensive vacuum tubes and had very limited clinical application. In the 1920s, W. T. Bovie developed a low-cost spark-gap generator. The potential of this device for use in surgery was recognized by Harvey Cushing during a demonstration in 1926, and the first practical electrosurgery units were soon in use.

Energy Sources

Electrocautery

The application of high-frequency alternating current is now known variously as electrocautery, electrosurgery, or simply "the Bovie." The current can be delivered through either a unipolar or a bipolar mechanism. In the unipolar application, the current is delivered by a generator via an application electrode, travels through the patient's body, and returns to a grounding pad. Without a grounding

pad the patient would suffer a thermal burn injury wherever the current seeks reentry. The area of contact is critical because heat is inversely related to the size of the application device. Accordingly, the tip of the device is typically small to generate heat efficiently, and the returning electrode is large to broadly disperse energy. Three other settings are pertinent: the frequency of the current (power setting), the activation time, and the characteristics of the waveform produced by the generator (intermittent or continuous).

In the "cut" mode, heat is generated quickly with minimal lateral spread. As a result, the device separates tissue without significant coagulation of underlying vessels. In the "coagulation" mode, the device generates less heat at a slower frequency with larger lateral thermal spread. As a consequence, tissue is desiccated and vessels become thrombosed.

Bipolar cautery creates a short circuit between the grasping tips of the instruments; thus, the circuit is completed through the grasped tissue between the tips. Because heat develops only within the short-circuited tissue, there is less lateral thermal spread and the mechanical advantage of tissue compression, as well as thermal coagulation.

Argon Beam Coagulator

The argon beam coagulator creates an electric circuit between the tip of the probe and the target tissue through a flowing stream of ionized argon gas. The electrical current is conducted to the tissue via the argon gas and produces thermal coagulation. The flow of the argon gas improves visibility and disperses any surface blood, thereby enhancing coagulation. Its applications in hepatic surgery are unparalleled.

Surgical Lasers

Lasers (i.e., light amplification by stimulated emission of radiation) are devices that produce an extremely intense and nearly nondivergent beam of monochromic radiation, usually in the visible region. When focused at close range, laser light is capable of producing intense heat with resultant coagulation. Lateral spread is minimal, and critically, the laser beam can be delivered through a fiber-optic system.

Based on power setting and the photon chosen, depth can be controlled. Penetration depth within tissue is most shallow with the argon laser, intermediate with the carbon dioxide (CO_2) laser, and greatest with the neodymium-yttrium aluminum garnet (Nd-YAG) laser. Photosensitizing agents provide an additional targeting advantage. The degree of absorption and thus destruction depends on the wavelength selected and the absorptive properties of the tissue based on density, fibrosis, and vascularity.

Photodynamic Therapy

A novel application of light energy is used in photodynamic therapy. A photosensitizer that is target cell specific is administered and subsequently concentrated in the tissue to be eradicated. The photosensitizing agent may then be activated with a light energy source to induce tissue destruction. Applications have been widespread.[209] Metaplastic cells, in particular, in Barrett's esophagus, may also be susceptible.[185]

Ultrasound

In addition to the diagnostic use of US at low frequency, delivery of high-frequency US can be used to separate and coagulate tissue. Focused acoustic waves are now used extensively in the treatment of renal calculi as extracorporeal shock wave lithotripsy. The focused energy produces a shock wave that results in fragmentation of the stones to a size that can be spontaneously passed.

Harmonic Scalpel

When US energy at very high frequency (55,000 Hz) is used, tissue can be separated with minimal peripheral damage. Such high-frequency energy creates vibration, friction, heat, and ultimately, tissue destruction.

High-Intensity Focused Ultrasound

When high-intensity US energy from multiple beams is focused at a point on a target tissue, heating and thermal necrosis result. None of the individual US beams are of sufficient magnitude to cause injury; only at the focus point does thermal injury result. As a result, subcutaneous nodules may be targeted without injury to skin, or nodules within the parenchyma of a solid organ may be destroyed without penetrating the surface. Thus far, however, the focal point is extremely small, which has limited its use.

Cavitation Devices

The CUSA, a cavitation US aspirator, uses lower-frequency US energy with concomitant aspiration. Fragmentation of high–water content tissue allows for parenchymal destruction while highlighting vascular structures and permitting their precise coagulation.

Radiofrequency Energy

High-frequency alternating current (350 to 500 kHz) may be used for tissue division, vessel sealing, or tissue ablation. Application of this energy source heats the target tissue and causes protein denaturization and necrosis. A feedback loop sensor discontinues the current at a selected point, thereby minimizing collateral damage. Its targeted use in modulating the lower esophageal sphincter for the treatment of reflux has been reported.[223]

Microwave Energy

Microwave energy (2450 MHz) can be delivered via a probe to a target tissue. This rapidly alternating electrical signal produces heat and thus coagulation necrosis.

Cryotherapy

At the other end of the temperature spectrum, cold temperatures destroy tissue with a cycle of freezing and

thawing—ice crystal formation in the freezing phase and disruption during the thawing phase. Thus far this modality has less utility because high vascular flow, especially in tumors, tends to siphon off the cold.

Image Guidance Systems

Recent developments in computation technology have fundamentally enhanced the role of medical imaging, from diagnostics described previously to computer-assisted surgery (CAS). During the last decade, medical imaging methods have grown from their initial use as physically based models of human anatomy to applied computer vision and graphic techniques for planning and analyzing surgical procedures. With rapid advances in high-speed computation, the task of assembling and visualizing clinical data has been greatly facilitated, thus creating new opportunities for real-time, interactive computer applications during surgical procedures.[40,142,197,212] This area of development, termed image-guided surgery, has slowly evolved into a field best called information-guided therapy (IGT) because it involves the use of a variety of data sources to implement the best therapeutic intervention. Such therapeutic interventions could conceivably range from biopsy, to simulation of tissue, to direct implantation of medication, to radiotherapy. Common to all these highly technical interventions is the need to precisely intervene with the therapeutic modality at a specific point.

However, the effective utilization of biomedical engineering, computation, and imaging concepts for IGT has not reached its full potential. Significant challenges remain in the development of basic scientific and mathematical frameworks that form the foundation for improving therapeutic interventions through the application of relevant information sources.

Significance

As stated in the National Institutes of Heath 1995 *Support for Bioengineering Research Report* (*http://grants.nih.gov/grants/becon/externalreport.html*), an appropriate use of technology would be to replace traditional invasive procedures with noninvasive techniques. The current interest in research in CAS, or IGT, can be attributed in part to considerable clinical interest in the well-recognized benefits of minimal access surgery (MAS), while remaining cognizant of its limitations.

Image-based surgical guidance, on the other hand, addresses these limitations. Image-guided surgical navigational systems have now become the standard of care for cranial neurosurgical procedures in which precise localization within and movement through the brain are of utmost importance.

Patient-specific image data sets such as CT or MRI, once correlated with fixed anatomic reference points, or fiducials, can provide surgeons with detailed spatial information about the region of interest. Surgeons can then use these images to precisely target and localize pathologies. Intraoperative computer-assisted imaging improves the surgeon's ability to follow preoperative plans by showing location and optimal direction. Thus, the addition of CAS provides the advantages of MAS with the added benefits of greater precision and an increased likelihood of complete and accurate resection. The junction between CAS and MAS presents research opportunities and challenges for imaging scientists and surgeons everywhere.

General Requirements

Patient-Specific Models

Unlike simulation, IGT requires that modeling data be matched specifically to the patient being treated because standard fabricated models based on typical anatomy are inadequate during actual surgical procedures on a specific patient. Patient-specific images can be generated preoperatively (e.g., by CT or MRI) or intraoperatively (e.g., by US or conventional radiography).

High Image Quality

IGT depends on spatially accurate models. Images require exceptional resolution in order to portray realistic and consistent information.

Real-Time Feedback

Current systems make the surgeon wait while new images are being segmented and updated. Thus, fast dynamic feedback is needed, and the latencies associated with visualization segmentation and registration should be minimized.

High Accuracy and Precision

A recent American Association of Neurological Surgeons survey of 250 neurosurgeons[177] disclosed that surgeons had little tolerance for error (1 to 2 mm accuracy in general, and 2 to 3 mm for spinal and orthopedic applications). All elements of visualization, registration, and tracking must be accurate and precise, with special attention paid to errors associated with intraoperative tissue deformation.

Repeatability and Robustness

IGT systems must be able to automatically incorporate a variety of data so that algorithms work consistently and reliably in any situation.

Correlation of Intraoperative Information with Preoperative Images

This requirement is a key area of interest to biomedical engineers and is especially critical for compensation of tissue deformation. Whether produced by microscopes, endoscopes, fluoroscopes, electrical recordings, physiologic simulation, or other imaging techniques, preoperative and intraoperative images and information need to be incorporated into and correlated by the surgical guidance system.

Intuitive Machine and User Interfaces

The most important part of any IGT system is its usability. The surgeon's attention must be focused on the patient and not on the details of the computational model.

Stereotactic Radiosurgery

Whereas laparoscopy has been the dominant arena for recent technologic development in general surgery, other surgical disciplines have used alternative minimally invasive solutions that follow the surgical theme of "image" and "manipulation" highlighted in this chapter. For example, endovascular interventions such as percutaneous coronary angioplasty, drug-eluting coronary stents, and aortic stent grafts have revolutionized the management of cardiovascular disease.[8,22,23] In the field of otolaryngology and neurosurgery, computerized image guidance systems have been used to accurately correlate intraoperatively encountered structures with preoperative images.[112,113] The discipline of stereotactic radiosurgery takes the concepts underlying image-guided surgery one step further.

Stereotactic radiosurgery uses precision targeting and large numbers of crossfired, highly collimated beams of high-energy ionizing radiation to noninvasively ablate tissue. Conceptualized in the 1950s by the Swedish neurosurgeon Lars Leksell, this technology has been used to treat/ablate a variety of benign and malignant intracranial lesions without an incision.[119] Lesioning of normal brain tissue such as the trigeminal nerve (trigeminal neuralgia), thalamus (tremor), and epileptic foci (intractable seizures) is an important clinical application of this technology.[34] Meanwhile, numerous studies have demonstrated that radiosurgery is an important treatment option for many otolaryngologic conditions, including skull base and head and neck tumors.[4,9,16,66] Most recently, radiosurgical techniques have been applied to the treatment of extracranial diseases, such as spinal tumors and lesions of the thoracic and abdominal cavities.[215,216] Many of the newest applications of stereotactic radiosurgery fall under the traditional realm of general surgery, including lung, liver, and pancreatic cancer.[78,152,154,171,175,206,224,235] As the scientific understanding and clinical practice of radiosurgery develop, such technology may become an increasingly valuable, minimally invasive option for treating a range of pediatric general surgical diseases. The purpose of this section is to review the principles and current application of stereotactic radiosurgery in children. In addition, this section will highlight the relatively new application of stereotactic radiosurgery to extracranial sites, with a focus on emerging scientific and technologic directions.

Radiobiology

Since Roentgen's discovery of x-rays in 1895, scientists and clinicians have studied the effects of ionizing radiation on biologic tissue, a field termed *radiobiology*. In 1906, Bergonié and Tribondeau performed experiments in which it was shown that immature, dividing cells were damaged at lower radiation doses than were mature, nondividing cells.[12] Their observations led to formation of the Bergonié-Tribondeau law, which states that ionizing radiation is more effective against cells that are undifferentiated and actively mitotic.[12] Subsequent generations of research have substantiated this law and further refined our current understanding of the biologic basis for radiotherapy.[19,117,119,198]

Both charged particles (alpha particles, proton beams, or electron beams) and high-energy light beams (gamma rays or x-rays) produce either direct or indirect damage to the DNA of target cells.[83] The densely ionizing nature of particulate radiation causes direct damage to cellular DNA. In contrast, the mechanism of action for most high-energy photon beams (x-rays) is ejection of electrons (radiolysis) from the cell's constituent molecules (mostly water).[82,124] The ejected electrons can damage DNA directly and cause the formation of cell-damaging free radicals. The later entity may combine with other free radicals to form new molecules, such as hydrogen peroxide, that are toxic to vital cellular structures (membranes and lysozymes). These free radicals also have the potential to secondarily damage chromosomal DNA. There are a number of molecular mechanisms for such injury after high-energy irradiation: one involves loss of a nitrogenous base, a second involves damage to the hydrogen bond between the two strands of the DNA molecule, and a third involves damage to the DNA backbone.[82,124]

Damage to a single strand of a DNA molecule is of little consequence because it is usually reparable. However, if the effects of a radiation beam are sufficiently concentrated, two nearby single-strand breaks can produce an uncorrectable double-strand break.[176] During subsequent cycles of cell division, a critical level of genomic instability may lead to cell inactivation.[196] This postmitotic model for cell death is the prevailing mode, although apoptotic cell death may also occur if the damage to DNA initiates p53- and Bcl-2–dependent mechanisms. These mechanisms can begin a cascade that results in the activation of effector caspases, thereby targeting multiple critical cellular death substrates.[228] In addition, radiation damage may affect the rate of cell division and thus result in a delay (of cell division) and an accompanying decrease in the cell population. Finally, interphase death may occur if radiation kills the cells during the G_1, S, or G_2 phase. Cells are most radiosensitive during the G_2 and M phases.[228]

The amount of cellular damage induced by a particular form of radiation is related to the radiation's linear energy transfer (LET). LET describes the amount of energy that is transferred from the radiation beam to the tissue that it is directed through; it is calculated by dividing the energy deposited in kiloelectron volts by the distance traveled in micrometers.[82,83] X-rays and gamma rays are classified as having low LET because their electrons distribute over a greater distance in tissue. The LET level of radiation is important because equal doses of radiation with different LET levels produce a different biologic response. The term "relative biologic response" describes a measure of the comparative biologic effect between the more damaging heavy-particle and x-ray beams.[82]

Various physical, chemical, and biologic factors can influence the sensitivity of a given cell's response to radiation. The important physical factors that influence the

cellular response include the LET level and the dose rate of radiation.[198] Optimal LET is approximately 160 keV/μm, which produces the highest level of double-strand DNA breaks. Meanwhile, a higher dose rate of radiation prevents cells from repairing sublethal chromosomal damage.

Certain chemical factors termed radiosensitizers and radioprotectants modulate the effectiveness of radiation. The most potent radiosensitizer, oxygen, promotes the formation of indirectly damaging free radicals.[198] Hypoxic cells, as often seen in larger malignant tumors, are resistant to radiation.

Two vital biologic factors underlying the cellular response to high-energy radiation are the phase in the cell cycle and the capacity of a cell to repair sublethal damage. Cells in the G_2 and M phases are the most sensitive. Cells exposed to the same cumulative dose of radiation but undergoing multiple exposures in a process termed fractionation will have a higher survival rate than will cells exposed to the entire dose in one fraction or session.[117] This phenomenon stems from a cell's ability to repair sublethal damage before subsequent radiation exposure, and it forms an important theoretical basis for the effectiveness of radiosurgery.[117]

Radiotherapy and Fractionation

Radiation therapy, or *radiotherapy*, refers to the use of ionizing radiation for the treatment of pathologic disorders. The use of radiation to cure cancer was first reported in 1899, soon after Roentgen's discovery of x-rays in 1895.[35] In the 1930s, Coutard described the practice of "fractionation," which refers to the division of a total dose of radiation into multiple smaller doses, typically given on a daily basis.[35] Fractionation is a bedrock principle that underlies the field of radiotherapy.[117,118] By administering radiation in multiple daily fractions over the course of several weeks, it is possible to irradiate a tumor with a higher total dose while relatively sparing the surrounding normal tissue from the most injurious effects of treatment. The effect of radiation on tissues is dependent on several factors, commonly referred to as the four R's: repopulation, redistribution, repair, and reoxygenation.[218] Repopulation refers to the division and consequent multiplication of surviving cells in the tumor and adjacent normal tissue. Ideally, the only repopulation that would occur after treatment would be that of adjacent normal tissue. Redistribution refers to the death of cells in their radiosensitive phase (G_2 and M) and survival of cells in the S phase. Ideally, radiation is administered when tumor cells are in their radiosensitive phase and the adjacent normal tissue is in the less sensitive S phase of the cell cycle. Repair of sublethal damage between fractionated doses of radiation is dependent on oxygen.[218] Tumor cells are hypoxic and therefore less able to repair their DNA. Furthermore, oxygen is important in the free radical mechanism that radiation uses to kill a tumor. The manner in which tumor cells gain access to oxygen and become more radiosensitive between treatments is called reoxygenation. Although the exact mechanism is unclear, hypoxic regions of a tumor often tend to become better oxygenated, and therefore more radiosensitive, over a prolonged period. This phenomenon can make fractionated treatment more effective than single-dose radiotherapy under some clinical circumstances.[218] Overall, fractionation is an extremely important concept in radiotherapy inasmuch as standard techniques expose both normal and pathologic tissue to irradiation. By fractionating therapy, normal tissue should recover while pathologic tissue is destroyed. Although fractionation regimens differ depending on the specific pathology, current regimens often involve up to 30 treatments.[35]

Before the 1950s, radiotherapy machines were capable of delivering only relatively low-energy x-rays characterized by rapid energy loss and shallow depth penetration.[35] However, newer machines capable of delivering megaelectron volts (MeV) of x-rays were developed that allowed greater depth penetration and thereby facilitated the treatment of more deep-seated lesions. Today, radiotherapy is primarily delivered with linear accelerators, or linacs, which use electromagnetic waves to accelerate charged particles through a linear tube. These particles emerge from the linac to strike a metal foil and produce x-rays. This process is termed *bremsstrahlung*.[35] Less commonly, cobalt 60 units, which use radioactive isotopes as a high-energy radiation source, are used to deliver radiotherapy.[35] These units have a relatively shallow maximal dose depth of approximately 0.5 cm, thus making them less useful for deeper lesions. Radiotherapy is a well-established treatment of intracranial and extracranial pathologies.[4,9,34,116,119] The medical literature regarding its use is extensive and therefore beyond the scope of this review.

Stereotactic Radiosurgery

Stereotactic radiosurgery refers to the method and corresponding technology for delivering a single high dose of radiation to a well-defined target. It has the potential advantage of delivering a much larger radiation dose to a pathologic lesion without exceeding the radiation tolerance of the surrounding normal tissue. This single, or limited, dose treatment of a small volume of tissue is achieved by targeting the tissue with large numbers of intersecting beams of radiation. "Stereotactic" refers to the fact that radiosurgery uses computer algorithms to coordinate the patient's real-time anatomy in the treatment suite with a preoperative image to allow precise targeting. To achieve this goal, the patient's anatomy is fixed with a stereotactic frame.[34,35] The preoperative images are then taken with the frame in place, and the patient's anatomy is mapped in relation to the frame. This stereotactic frame is rigidly fixed to the patient's skull, thereby limiting movement of the target anatomy. In addition, the frame serves as an external fiducial system that correlates the coordinates of the target tissues determined during preoperative imaging and planning. Leksell first described this technique in 1951 and showed that there was an exponential relationship between dose and the time over which necrosis developed. By using multiple beams at different angles, one can achieve a steep falloff in dose at the periphery of the target volume. For this reason, appropriate definition of the target volume in radiosurgery is of utmost importance. Limited fractionation can now be used in conjunction with stereotactic radiosurgery in a

procedure that has recently been termed fractionated or staged radiosurgery.[35] The concept of staging capitalizes on one of the "four R's" by giving surrounding normal tissue time to repair. Because of the cellular makeup, single large fractions tend to be effective on slowly proliferating tissue, such as benign tumors and arteriovenous malformations (AVMs).[35] In contrast, techniques involving staged radiosurgery allow for some normal tissue repair and may be advantageous when ablating larger-volume tumors or lesions that are adjacent to critical normal anatomy.

Currently, several classes of stereotactic radiosurgery systems are in use, including heavy-particle radiosurgery systems, gamma knife radiosurgery, linear accelerator radiosurgery, and frameless image-guided radiosurgery.

Stereotactic Radiosurgery Systems: Current Technology

Heavy-Particle Radiosurgery: Proton-based radiosurgery systems are some of the earliest stereotactic radiosurgery systems used.[55,56,134,135] Charged particles (proton or helium ions) have a unique advantage over photons with respect to radiosurgery.[136] Radiosurgery using photons relies on systems of crossfiring beams from multiple directions to achieve high target tissue radiation delivery while minimizing the radiation exposure of surrounding normal tissue as photons deposit energy along the entire path of the beam. In contrast, charged particles deliver energy in a nonuniform pattern along their beam length. Specifically, they produce a region of intermediate energy dose at the entry site, followed by a zone of high-dose energy termed the Bragg ionization peak, and then followed by an exit dose of minimal energy.[35] The Bragg ionization peak can be adjusted to precisely deliver peak energy levels to a targeted tissue area.[136] Although this phenomenon is advantageous, heavy-particle radiosurgery systems have several disadvantages that have limited their widespread use. Specifically, the systems are very expensive to construct and maintain and require a working cyclotron. Furthermore, such systems require beam-modifying devices that must be custom made for each patient and require the patient to wear an immobilizing plastic mask or bite block to achieve fixation. Because of these limitations, heavy-particle radiosurgery is currently limited to two active sites in the United States and is used solely for intracranial lesions.[35]

Gamma Knife Radiosurgery: In contrast to heavy-particle radiosurgery systems, gamma knife radiosurgery is significantly less expensive and easier to use. First developed by Leksell in 1967, the Leksell Gamma Knife (Elekta Instruments, Inc., Norcross, GA) uses cobalt 60 as a radiation source.[35] The original gamma knife was used for pallidotomy in the treatment of Parkinson's disease and to treat intracranial tumors and vascular malformations.[34,35,67,90,101] Because the Gamma Knife uses a stereotactic frame, radiosurgical treatments with this system are not fractionated and primarily consist of a one-time therapeutic session.[113] Figure 4-8A and B depicts the Leksell Gamma Knife.

Linear Accelerator Radiosurgery: Linear accelerators, or linacs, have long been the mainstay of standard fractionated

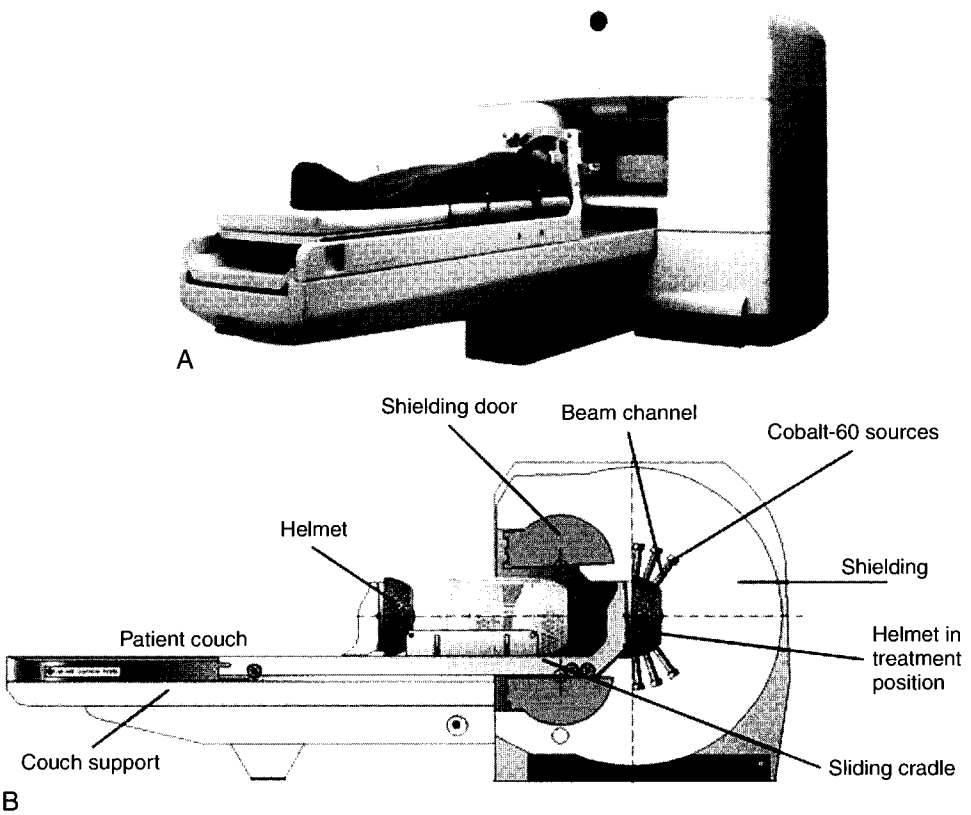


Figure 4–8 *A,* Leksell Gamma Knife. (Courtesy of Elekta Instruments, Inc., Norcross, GA.) *B,* Leksell Gamma Knife layout (*http://www.sh.Isuhsc.edu/neurosurgery/gammaknife/gamma-knife/*).

radiotherapy[5,18,39,116] and were modified for radiosurgery in 1982.[35] Linac radiosurgery has subsequently become a cost-effective and widely used alternative to gamma knife radiosurgery. When used for radiosurgery, linacs crossfire a photon beam by moving in multiple arc-shaped paths around the patient's head. The area of crossfire where the multiple fired beams intersect receives a high amount of radiation, with minimal exposure to surrounding normal tissue.[35] Patients treated with linac radiosurgery must also wear a stereotactic frame fixed to the skull for preoperative imaging and therapy. Currently, linac radiosurgery is the predominant modality in the United States, with approximately six times more active centers than gamma knife facilities.[35]

Frameless Image-Guided Radiosurgery: Recently, a novel modified version of linac radiosurgery has been developed that enables frameless image-guided radiosurgery. The system, commercially available as the CyberKnife (Accuray, Inc., Sunnyvale, CA), uses a lightweight linac unit designed for radiosurgery mounted on a highly maneuverable robotic arm.[33] The robotic arm can position and point the linac with 6 degrees of freedom and 0.3-mm precision. In addition, the CyberKnife system features image guidance, which eliminates the need for skeletal fixation.[34,36] The CyberKnife acquires a series of stereoscopic radiographs that identify a preoperatively placed gold fiducial. This fiducial is placed under local anesthesia during the preoperative imaging and planning sessions to allow the system to correlate the patient's target anatomy with the preoperative image for treatment. By actively acquiring radiographs during the treatment session, the system is able to track and follow the target anatomy in nearly real time during treatment.[33,34] With an image guidance system, the CyberKnife functions without a fixed stereotactic frame, thereby enabling fractionation (hypofractionated radiosurgery) of treatment, as well as extracorporeal stereotactic use. In pediatric surgery, this may be a significant technical advantage because it may enable the use of radiosurgery for the treatment of intrathoracic and intra-abdominal pathology (Fig. 4-9).

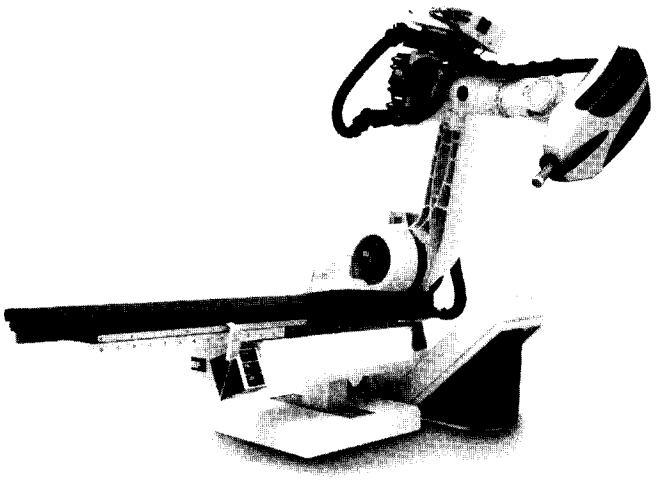


Figure 4–9 CyberKnife System *(http://www.sky.sannet.ne.jp/ybaba/main.html).*

Stereotactic Radiosurgery in Children

Stereotactic radiosurgery of intracranial lesions has been a well-established treatment modality for many years. From the viewpoint of radiosurgery, the fact that the intracranial contents are relatively static results in essentially nonmobile target tissues, thus enabling the delivery of high radiation doses in one or few treatment fractions with minimal risk to adjacent normal tissue. Accuracy is maximized by the use of stereotactic head frames that fix the skull in a given position to allow precise targeting of the desired tissue. This has led to the widespread use of stereotactic radiosurgical techniques in adults for the treatment of benign and malignant otolaryngologic[4,39,41,131,132] and neurosurgical[67,68,80,129,168,201] lesions that are contained within the rigid confines of the skull. Multiple groups have reported the safe and effective use of stereotactic radiosurgery for the treatment of malignant lesions of the brain and neck in children.* In addition to pediatric brain tumors, stereotactic radiosurgery has also been described for the treatment of nonmalignant intracranial lesions in children. The use of radiosurgery for the treatment of cerebral AVMs has been well documented.[102,133,138,156,200] In a series of 30 children with intracranial AVMs (mean age, 11.2 years), the overall obliteration rate after radiosurgery was 35%. The authors concluded that stereotactic radiosurgery was an effective treatment option with acceptably low complication rates for children with cerebral AVMs.[200]

When compared with the adult population, the experience with stereotactic radiosurgery in children is still somewhat limited. Early reports highlight the safety and efficacy of radiosurgery as a treatment modality, but clinical follow-up is still early, with many of the studies limiting the use of radiosurgery to surgically unresectable disease. Despite the relatively limited experience, the use of stereotactic radiosurgery in children may offer several theoretical advantages specific to the pediatric population. In comparison to standard, fractionated radiotherapy, stereotactic radiosurgical techniques deliver conformal radiation treatment with millimeter versus centimeter accuracy. In pediatric patients, the distance between normal and pathologic tissue may be very small. In addition, the developing brain in a child may be more sensitive to the effects of ionizing radiation than adult brains are. Potential cognitive and endocrine disabilities have been described in children after delivery of radiotherapy to the brain.[69,70,201] These concerns have largely limited the use of radiation for the treatment of intracranial tumors in infants. Therefore, the improved accuracy provided by stereotactic radiosurgery may be particularly important in the pediatric population.

In addition to accuracy, stereotactic radiosurgical techniques differ from radiotherapy in that they involve only one to very few treatment sessions. Standard, fractionated radiotherapy often requires tens of treatment sessions to maximize the beneficial effects of the treatment while minimizing the harmful effects to normal tissue. In children, multiple treatment sessions may be a significant challenge.

*See references 14, 20, 43, 51, 59, 93, 95, 184, 205, 231, 234, 244.

In smaller children, sedation or anesthesia may be necessary to avoid movement. Such interventions are not without risk, and limiting the number of treatment sessions may serve to minimize the overall risk to pediatric patients.

Although the advantages of stereotactic radiosurgery in children appear promising, there are also specific disadvantages and limitations that must be overcome. Radiosurgical techniques generally use a stereotactic frame to coordinate preoperative imaging with actual radiation delivery. However, these frames must be secured to the skull with pins and screws. In adults, this can often be performed under local anesthesia, but children probably need significant sedation and possibly general anesthesia. Furthermore, an infant's skull is soft and less rigid because the cranial sutures have not yet fused, and standard stereotactic frames often cannot be applied. Similarly, radiosurgery treatment sessions require the patient to remain still for the system to accurately deliver the radiation treatment. Adults are able to cooperate and do not need sedation; however, younger children and infants may require conscious sedation or general anesthesia. Although this drawback is limited by the relatively few sessions needed with radiosurgery, it still diminishes the minimally invasive nature of the therapy in comparison to its application in adults.

Recently, frameless, image-guided stereotactic radiosurgery has been performed with the CyberKnife system using a linac mounted on a robotic arm to deliver radiation energy. In addition, the system uses real-time image guidance to track the movements of a patient's anatomy during the treatment session. Consequently, stereotactic frames are not used with this form of radiosurgery. Recently, Giller et al. described the use of this system in children.[69,70] They used the CyberKnife system in 21 children with brain tumors; their ages ranged from 8 months to 16 years.[69] There were no procedure-related deaths or complications, and local control was achieved in over half the patients. Seventy-one percent of patients received only one treatment session and 38% did not require general anesthesia. None of the patients required rigid skull fixation.[69] In an additional report, the same group highlighted the use of the CyberKnife system to perform radiosurgery in five infants.[70] Although standard stereotactic frames were not required, patient immobilization was aided by general anesthesia, form-fitting head supports, face masks, and body molds. No treatment-related toxicity was encountered, and the authors concluded that "radiosurgery with minimal toxicity can be delivered to infants by use of a robotically controlled system that does not require rigid fixation."[69]

Extracranial Stereotactic Radiosurgery—Implications for General Surgery

Whereas the use of stereotactic radiosurgery for intracranial lesions has been well established, its use for the treatment of extracranial lesions, specifically, intrathoracic and intra-abdominal pathology, is still in its infancy. Although the intracranial contents can easily be immobilized with stereotactic frames, the abdominal and thoracic organs are subject to significant movement because of respiration, peristalsis, and other factors. As a result, only a small body of literature is currently available on the application of stereotactic radiosurgery for extracranial lesions. Recently, several reports have described the efficacy of stereotactic radiosurgery for the treatment of lesions in the liver,[114,216,217,238-241] pancreas,[141,153,154] lung,[236,238,240] and kidney[171,175]—anatomic areas that have traditionally been in the domain of general surgeons. Novel image guidance technologies, as well as soft tissue immobilization devices, have been used to make these therapies possible.[35,152,216,235]

At this time, the majority of the clinical literature is represented by case reports and series detailing the safety and feasibility of extracranial radiosurgery. In addition, many of the reports focus on the technical and engineering aspects of applying radiosurgical techniques to extracranial targets with little data on patient outcomes. All the reports have focused on the adult patient population. However, despite this inexperience, the technology surrounding stereotactic radiosurgery is rapidly developing and shows significant promise for minimally invasive treatment of potentially poorly accessible lesions. Newer systems such as the frameless image-guided CyberKnife system may someday enable the minimally invasive treatment of a variety of pediatric malignancies.

Radioimmunoguided Surgery

Antibodies labeled with radionuclides, when injected systemically, may bind specifically to tumors and thereby allow gamma probe detection.[125,190,204] For the most part, nonspecific binding and systemic persistence have minimized the signal-to-noise ratio, thus limiting this approach. Recently, the Food and Drug Administration (FDA) has approved several new promising radiolabeled antibodies to aid in the identification of occult metastases in patients with functioning endocrine tumors and in the evaluation of lymph node involvement in breast cancer and melanoma.

Surgical Robotics

Innovations in endoscopic technique and equipment continue to broaden the range of applications in MAS. However, many MAS procedures have yet to replace the traditional open approach. Difficulties remain in achieving dexterity and precision of instrument control within the confines of a limited operating space. This problem is further compounded by operating from a 2-D video image. Robotic surgical systems have now evolved that may address these limitations.

Since their introduction in the late 1990s, the use of computer-enhanced robotic surgical systems has grown rapidly. Originally conceived to facilitate battlefield surgery, these systems are now used to enable the performance of complex MAS procedures.* In children, early reports indicate that surgical robots can complete common and

*See references 7, 10, 54, 57, 61, 86, 103, 121, 147, 148, 183, 208.

relatively simple pediatric surgical procedures.[79,88] More recently, the use of robotic surgical systems has been described in multiple surgical disciplines, including pediatric surgery, pediatric urology, and pediatric cardiothoracic surgery.[128,140] In addition, complex, technically challenging procedures, such as robot-assisted fetal surgery, have been reported in animal models.[1,96,97,139,143]

Limitations of Standard Minimal Access Surgery Techniques and Technology

Although MAS techniques have revolutionized many operations, they have certain unique complexities not present with conventional open surgery. It is useful to highlight the specific technical challenges that surgical robots can address.

Movement Limitation

MAS instruments work through the body wall. Ports act as pivot points that reverse the direction of motion of the instrument tip in relation to the motion of the instrument handle. To move the instrument tip to the left within the body cavity, the hand of the surgeon must move to the right outside the body. This reversal of movement requires nonintuitive instrument control that is mentally taxing, especially as the complexity of the surgical task increases.

The majority of MAS instruments consist of an end-effector mounted to the tip of a long rigid shaft. The endoscopic cannula allows these instruments to pivot around the fixed point within the body wall, but motion is restricted laterally. The 6 degrees of freedom of position and orientation (defined as motion along the x-, y-, and z-axes and rotation about each of these axes) of open instruments are therefore reduced to 4 degrees of motion (pitch, yaw, roll, and insertion) for MAS procedures (Fig. 4-10A). An additional 2 degrees of freedom could be restored to MAS instruments by constructing articulations at the distal end, past the location of the cannula pivot point (Fig. 4-10B). However, precise and dynamic control of these distal articulations during an operative procedure would be difficult to coordinate without computer-assisted control.

Haptic Limitations

The long shafts of MAS instruments force the surgeon's hands to be separated from the operative anatomy, which significantly decreases tactile sensation and force reflection. The extended instrument length also magnifies any existing hand tremor. Furthermore, the excursion of an instrument tip is highly dependent on its depth of insertion. For instance, an instrument that is shallowly inserted requires comparatively large hand movements to accomplish a given instrument movement inside the body, whereas a deeply inserted instrument requires much less hand movement to sweep the instrument tip around. Consequently, the dynamics of the instrument change constantly throughout a procedure. These factors can lead to less precise and predictable movements than is the case with standard, open surgical techniques.

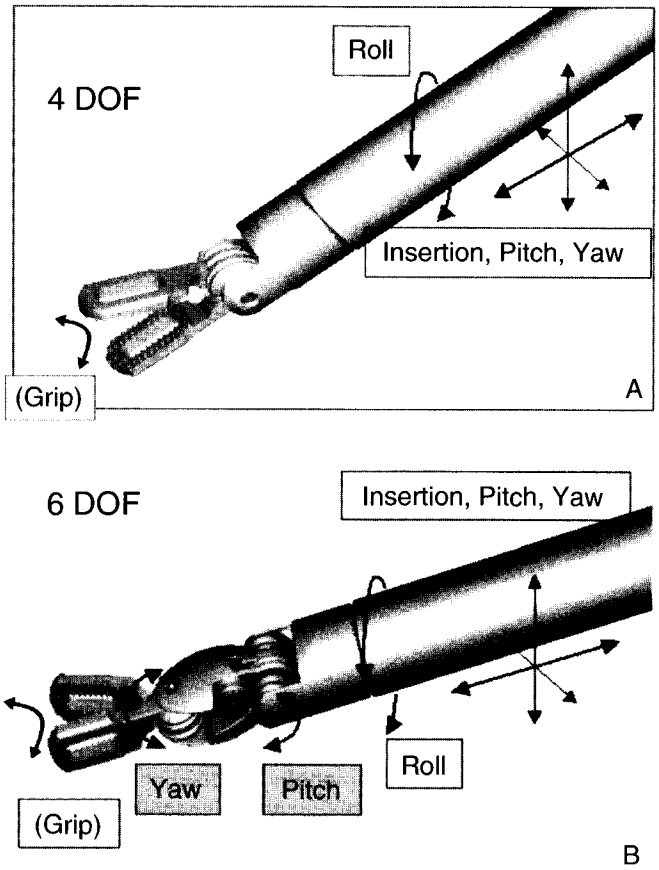


Figure 4-10 *A*, Traditional 4-degree-of-freedom (DOF) endoscopic instrument. *B*, Fully articulated 6-DOF robotic instrument. (Courtesy of Intuitive Surgical, Sunnyvale, CA.)

Visual Limitations

The introduction of an endoscope requires the surgeon to be guided by a video image instead of direct vision. The video monitor is often located on the far side of the patient, and the difference in orientation between the endoscope, instruments, and monitor requires the surgeon to perform a difficult mental transformation between the visual and motor coordinate frame.[214] This problem is further exacerbated when an angled endoscope is used.

Conventional endoscopes are built around a single lens train that displays images in a flat 2-D format. This removes many of the depth cues of normal binocular vision, thereby complicating tasks such as dissection between tissue planes. Some stereoscopic vision systems exist, but their performance is limited by the resolution and contrast characteristics of the endoscopes themselves, as well as display technologies. In addition, conventional endoscopes often require a dedicated assistant to hold and manipulate them. The natural tremors and movements of the assistant are exacerbated by the magnified image.

Robotic Technology in Surgery

For several decades, robots have served in a variety of applications such as manufacturing, deep-sea exploration,

munitions detonation, military surveillance, and entertainment. In contrast, the use of robotic technology in surgery is still a relatively young field. Improvements in mechanical design, kinematics, and control algorithms originally created for industrial robots are directly applicable to surgical robotics.

The first recorded application of surgical robotics was for CT-guided stereotactic brain biopsy in 1987.[242] Since then, technologic advancements have led to the development of several different robotic systems. These systems vary significantly in complexity and function.

Classification of Robotic Surgical Systems

One method of classifying robots is by their level of autonomy. Three types of robots are currently used in surgery: autonomous robots, surgical assist devices, and teleoperators (Table 4-2).

An autonomously operating robot carries out a preoperative plan without any immediate control from the surgeon. The tasks performed are typically focused or repetitive but require a degree of precision not attainable by human hands. An example is the Robodoc system used in orthopedic surgery to accurately mill out the femoral canal for hip implants.[11] Another example is the CyberKnife system, which consists of a linac mounted on a robotic arm to precisely deliver radiotherapy to intracranial and spinal tumors.[2,120]

The second class of robots is surgical assist devices, where the surgeon and robot share control. The most well-known example of this group is the AESOP unit (Automatic Endoscopic System for Optimal Positioning; Computer Motion, Inc., Goleta, CA). This system permits the surgeon to attach an endoscope to a robotic arm, which provides a steady image by eliminating the natural movements inherent in a live camera holder. The surgeon is then able to reposition the camera by voice commands. Today, the AESOP has been used by many different surgical disciplines, including general surgery,[6,108] gynecologic surgery,[149] cardiothoracic surgery,[160] and urology.[130]

The final class consists of teleoperator robots, whose every function is explicitly controlled by the surgeon. The hand motions of the surgeon at a control console are tracked by an electronic controller and then relayed to a slave robot so that the instrument tips perfectly mirror every movement of the surgeon. Because the control console is physically separated from the slave robot, these systems are referred to as teleoperators. All the recent advances in robot-assisted surgery have involved this latter class of machines.

TABLE 4-2 Classification of Robotic Surgical Systems

Type of System	Definition	Example
Autonomous	System carries out treatment without immediate input from the surgeon	CyberKnife Robodoc
Surgical assist	Surgeon and robot share control	Aesop
Teleoperators	Input from the surgeon directs movement of instruments	Intuitive Surgical da Vinci System Computer Motion Zeus System

History of Teleoperators

The foundation of teleoperator surgical systems can be traced back to the 1970s, when the U.S. National Aeronautics and Space Administration (NASA) began the development of telepresence surgical systems for use in space to accommodate emergency surgery for individuals living in a space station. In the late 1980s and early 1990s the goal was to develop systems capable of battlefield surgery, where surgeons well behind the front lines could operate on injured troops via robots installed on armored vehicles. These projects attempted to develop a form of telemanipulator robot in which the motions of a human operator are translated into movements of mechanical arms some distance away. Although the application of such "master-slave" systems to surgical operations was a revolutionary idea, examples of this technology were already being used in a variety of other industries. The first mechanical master-slave system was developed in 1948 by Raymond Goertz at Argonne National Laboratories. This robot, named the M1, used a series of steel cables and mechanical linkages to connect a master manipulator controlled by a human operator to an identical slave manipulator on the other side of a lead glass barrier for protection from radioactive exposure.

The Stanford Research Institute[72] (now SRI International, Stanford, CA) developed the first master-slave telepresence surgery system capable of performing operations. Consisting of a surgeon's workstation and a remote surgical unit, this system was designed to perform remote, open battlefield surgery. It featured remote articulating robotic arms, stereoscopic imaging, basic force feedback, and an ergonomic design. Although this system was never fully developed, it formed the foundation for the commercial systems in use today.

Current Status of Robotic Technology in Pediatric Surgery

Currently, the use of two robotic surgical systems has been reported in the pediatric surgical literature; the Zeus System (formerly Computer Motion, Goleta, CA; now operated by Intuitive Surgical, Sunnyvale, CA) and the da Vinci Surgical System (Intuitive Surgical). Both systems are classified as teleoperators. The two companies recently merged, and it is predicted that the da Vinci system will become the predominant robotic operative platform. However, at the current time, both systems remain in active clinical use.

Even though these systems are popularly referred to as surgical robots, this is a misnomer because "robot" implies autonomous movement. Neither the da Vinci nor the Zeus system operates without the immediate control of a surgeon. A better term may be "computer-enhanced telemanipulators." However, for the sake of consistency

with the published literature, this chapter will continue to refer to such systems as robots.

The Zeus System

The Zeus system consists of a surgeon's console and three robotic arms (Fig. 4-11A and B). The surgeon operates from a console several feet away from the operating table and uses hand-held manipulators to control the two robotic arms and surgical instruments, a foot pedal to activate the computer-driven system, and voice commands to direct a camera controlled by an AESOP arm.[96] Like the da Vinci system, the Zeus system offers tremor reduction and motion scaling.

The Zeus system consists of three modular, freestanding robotic arms that are attached to the operating table. This design allows the system to be oriented to many different configurations. The Zeus system also features 5-mm instruments capable of increased articulation through the Zeus Microwrist. This joint provides the instrument with an additional degree of freedom at the wrist, for a total of 6 degrees of freedom. More recently, 3.5-mm instruments have been developed. These instruments feature a small diameter and tip size, thus making them particularly useful in pediatric surgery. The Zeus system accommodates a variety of visualization options (3-D and 2-D) and telescope sizes.

The Zeus system has received generalized clearance for surgery under Conformité Européenne (CE) guidelines. In the United States, the Zeus system received FDA clearance for general laparoscopy and has been used for thoracic and cardiac procedures.

The da Vinci Surgical System

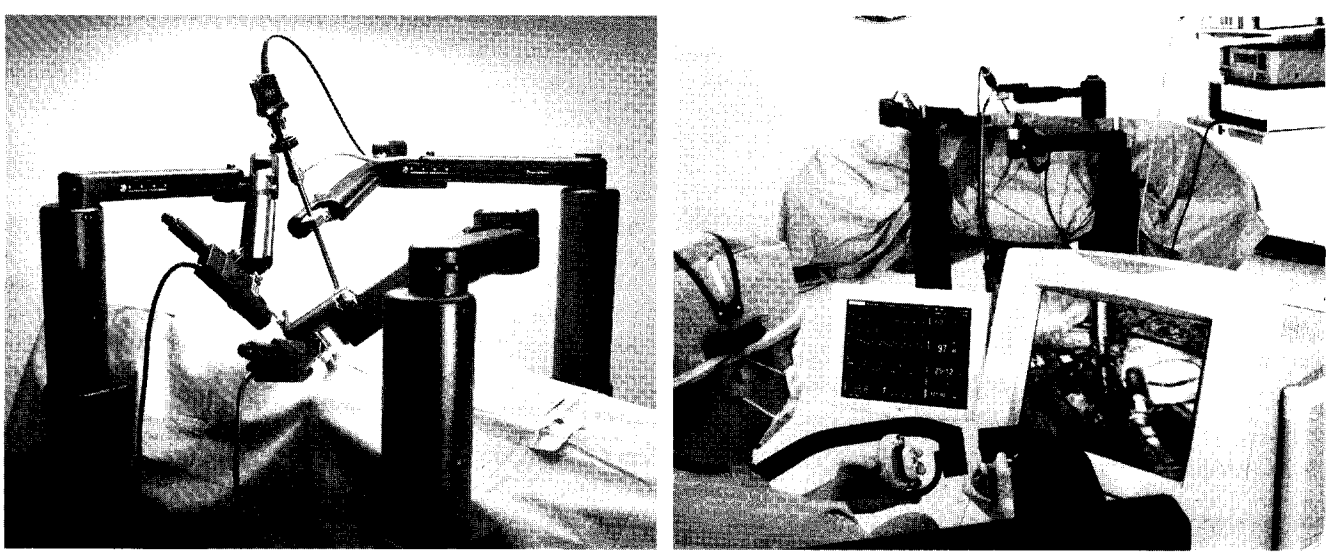
The da Vinci system consists of two major components[140] (Fig. 4-12A and B). The first component is the surgeon's console, which houses the visual display system, the surgeon's control handles, and the user interface panels. The second component is the patient side cart, which consists of two to three arms that control the operative instruments and another arm that controls the video endoscope.[50]

The operating surgeon is seated at the surgeon's console, which can be located up to 10 m away from the operating table. Within the console are located the surgeon's control handles, or masters, which act as high-resolution input devices that read the position, orientation, and grip commands from the surgeon's fingertips. This control system also allows for computer enhancement of functions such as motion scaling and tremor reduction.

The image of the operative site is projected to the surgeon through a high-resolution stereo display system that uses two medical-grade cathode ray tube (CRT) monitors to display a separate image to each of the surgeon's eyes. The surgeon's brain then fuses the two separate images into a virtual 3-D construct. The image plane of the stereo viewer is superimposed over the range of motion of the masters, which restores visual alignment and hand-eye coordination. In addition, because the image of the endoscopic instrument tips is overlaid on top of where surgeons sense their hands, the end effect is that surgeons feel that their hands are virtually inside the patient's body. For pediatric surgical applications, a new 2-D, 5-mm endoscope has been developed.

The standard da Vinci instrument platform consists of an array of 8.5-mm-diameter instruments. These instruments provide 7 degrees of freedom via a cable-driven system. Recently, a set of 5-mm instruments has become available. These instruments use a new "snake wrist" design and also provide 7 degrees of freedom (Fig. 4-12C).

Since its inception in 1995, the da Vinci system has received generalized clearance under European CE



A B

Figure 4–11 *A,* The Computer Motion Zeus robotic surgical system. *B,* The Zeus surgeon's console with its video display and master controls. (Courtesy of Intuitive Surgical, Sunnyvale, CA.)

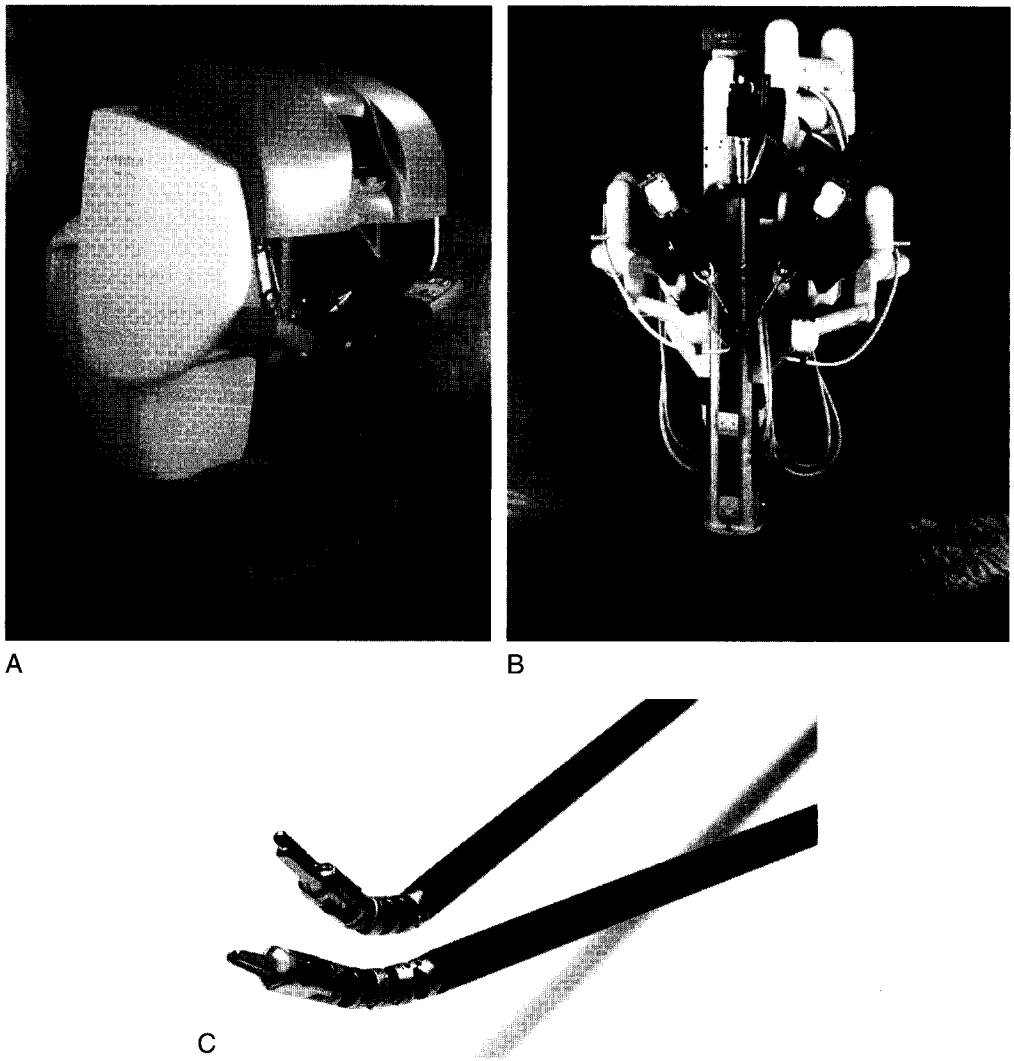


Figure 4-12 The Intuitive Surgical da Vinci robotic surgical system composed of a surgeon's console (*A*) and a patient-side cart (*B*). *C*, Articulated 5-mm robotic instrument. (Courtesy of Intuitive Surgical, Sunnyvale, CA.)

guidelines for all surgical procedures; in the United States it has received clearance for general surgery, thoracic surgery, and urologic procedures. In addition, the da Vinci system recently received FDA clearance for cardiac procedures involving a cardiotomy.

Current Advantages and Limitations of Robotic Pediatric Surgery

The utility of the different robotic surgical systems is highly influenced by the smaller size of pediatric patients and the reconstructive nature of many pediatric surgical procedures. Overall, the advantages of robotic systems stem from technical features and capabilities that directly address many of the limitations of standard endoscopic techniques and equipment. Unlike conventional laparoscopic instrumentation, which requires manipulation in reverse, movement of the robotic device allows the instruments to directly track the movement of the surgeon's hands. Intuitive nonreversed instrument control is therefore restored while preserving the minimal access nature of the approach. The intuitive control of the instruments is particularly advantageous for novice laparoscopists.

In infants and neonates, the use of a magnified image via operating loupes or endoscopes is often necessary to provide more accurate visualization of tiny structures.[207] This enhanced visualization is taken a step further with robotic systems because they are capable of providing a highly magnified 3-D image. The 3-D vision system adds an additional measure of safety and surgical control beyond what is available with the traditional endoscope. The 3-D display improves depth perception, and the ability to magnify images by a factor of 10 allows extremely sensitive and accurate surgical manipulation. The alignment of the visual axis with the surgeon's hands in the console further enhances hand-eye coordination to a degree uncommon in traditional laparoscopic surgery.

Similarly, the presence of a computer control system enables electronic tremor filtration, which makes the motion of the endoscope and the instrument tips steadier than with the unassisted hand. In addition, the systems allow for variable motion scaling from the surgeon's hand to the instrument tips. For instance, a 3:1 scale factor converts 3 cm of movement of the surgeon's hand into 1 cm of motion at the instrument tip. In combination with image magnification from the video endoscope, motion

scaling makes delicate motions in smaller anatomic areas easier to perform and more precise.[88]

Both systems use instruments that are engineered with articulations at the distal end, or "wrist," which increases their dexterity in comparison to traditional MAS tools. This technology permits a larger range of motion and rotation, similar to the natural range of articulation of the human wrist, and may be particularly helpful when working space is limited. Specifically, the da Vinci system offers instruments with 7 degrees of freedom, including grip, whereas the Zeus system features instruments capable of 6 degrees of freedom, including grip. Standard laparoscopic instruments are capable of only 5 degrees of freedom, including grip. This increased dexterity may be particularly advantageous during complex, reconstructive operations that require fine dissection and intracorporeal suturing.

Finally, by separating the surgeon from the patient, teleoperator systems feature ergonomically designed consoles that may decrease the fatigue often associated with long MAS procedures. This may become a more significant issue as the field of pediatric bariatric surgery develops because of the larger size and thicker body walls of adolescent bariatric patients. Table 4-3 details the potential advantages of robotic surgical systems in relation to the technical challenges of standard laparoscopic techniques.

Although robotic surgical systems provide several key advantages over standard MAS, a number of technologic limitations are specific to pediatric surgery. First and foremost is the size of the robotic systems. When compared with many pediatric surgical patients, the size of the da Vinci surgical cart or the Zeus modular robotic arms may be overwhelming. This size discrepancy may restrict a bedside surgical assistant's access to the patient while the arms are in use and may require the anesthesiology team to make special preparations to ensure prompt access to the patient's airway.[207]

The size and variety of available robotic instruments are limited in comparison to those offered for standard laparoscopy. Currently, the da Vinci surgical system is the only platform undergoing further development at the industry level. Recently, a new suite of 5-mm instruments with 7 degrees of freedom has been introduced for use with this system. Although these instruments represent a significant improvement over the original 8.5-mm instruments with respect to diameter, the number of instruments offered is still somewhat limited. Furthermore, these instruments use a new "snake wrist" architecture that requires slightly more intracorporeal working room to take full advantage of their enhanced dexterity. Specifically, the instruments are limited by a greater than 10-mm distance from the distal articulating joint, or wrist, and the instrument tip. Similarly, the Zeus system offers several 5-mm instruments capable of 6 degrees of freedom and features a shorter distance between the distal articulating joint and the instrument tip, thus allowing them to function at full capacity in a smaller working area. However, this is accomplished by giving up 1 degree of freedom. Unfortunately, no new resources will be applied to further develop the Zeus system since the corporate merger.

Finally, a number of general limitations currently inherent in the available robotic surgical systems must be overcome before they are universally accepted in pediatric surgery, including the high initial cost of the robotic systems and the relatively high recurring cost of the instruments and maintenance.[140] In addition, neither system offers true haptic feedback.[207] Even though such feedback is reduced in standard MAS in comparison to open procedures, it is further reduced with the robotic interface. This disadvantage is partially compensated for by the improved visualization offered by the robotic systems, but it remains a significant drawback when precise surgical dissection is required.

Finally, the robotic systems require additional, specialized training for the entire operating room team. This translates into robotic procedure times that are predictably longer than those of the conventional laparoscopic approach, at least until the surgical team becomes facile with use of the new technology. Even with an experienced team, setup times have been reported to require an additional 10 to 35 minutes at the beginning of each robot-assisted case.[207] Undoubtedly, many of these issues will be

TABLE 4-3 Potential Advantages of Current Teleoperator Systems

System	Potential Advantage	Standard MAS Limitation Addressed
Da Vinci	3-D visualization	2-D visualization with loss of depth perception
	Instruments with 6 degrees of freedom	Rigid laparoscopic instruments resulting in a high learning curve for complicated tasks such as intracorporeal suturing
	Motion scaling	Magnified tremor because of long length of laparoscopic instruments
	Tremor reduction	Magnified tremor because of long length of laparoscopic instruments
	Intuitive instrument control	Counterintuitive instrument tip control because of fulcrum effect of the laparoscopic cannula
Zeus	3-D visualization	2-D visualization with loss of depth perception
	Instruments with 5 degrees of freedom	Rigid laparoscopic instruments resulting in a high learning curve for complicated tasks such as intracorporeal suturing
	Motion scaling	Magnified tremor because of long length of laparoscopic instruments
	Tremor reduction	Magnified tremor because of long length of laparoscopic instruments
	Intuitive instrument control	Counterintuitive instrument tip control because of fulcrum effect of the laparoscopic cannula

MAS, minimal access surgery.

remedied in the next generation of equipment as the technology continues to improve.

Applications of Robotic Technology in Pediatric Surgery

To date, only a small body of literature regarding the application of robotic technology for pediatric surgical procedures has shown the feasibility of robot-assisted surgery. These reports detailed the completion of relatively routine laparoscopic operations in school-age children. More recently, procedures have been described in much younger patients in multiple fields, including pediatric general surgery, pediatric urology, and pediatric cardiothoracic surgery (Table 4-4). At this time the bulk of the literature represents class IV evidence consisting of case reports and case series, with no class I evidence. However, more recent reports call for a more critical analysis of the technology. The following sections detail the published literature to date, with a focus on current and future applications of robotic surgical systems in pediatric surgery.

Pediatric General Surgery

The first reports describing the use of robotic surgical systems for abdominal procedures in children were published by Gutt et al. and Heller et al. in 2002.[79,88] They described 11 children (mean age, 12 years; range, 7 to 16 years) who underwent either robot-assisted Thal or Nissen fundoplication for gastroesophageal reflux disease. In addition, two children underwent robot-assisted cholecystectomy for symptomatic cholelithiasis, and bilateral oophorectomy for gonadoblastoma was performed in one child. The da Vinci system with 8.5-mm instruments and a 12-mm endoscope was used. The mean operating time for fundoplication was 146 minutes (range, 105 to 180 minutes), with no significant intraoperative or postoperative complications.

In 2003, several authors reported additional case series describing the safety and feasibility of robot-assisted pediatric general surgery. Luebbe et al. described a series of 20 cases treated with the da Vinci system,[140] including 10 Nissen fundoplications (3 with gastrostomy and 1 with pyloroplasty), 3 cholecystectomies, 2 splenectomies, 1 urachus resection, 1 unilateral iliac and retroperitoneal lymphadenectomy, 1 biopsy of a presacral mass, 1 biopsy of a hepatic mass, 1 Gore-Tex patch repair of a Morgagni diaphragmatic hernia, and 1 biopsy of a benign mediastinal mass.[1,140] The mean age of the patients was 8.4 years, although the youngest patient was 4 months old and the smallest was 6.8 kg. The mean console operating time was 93 minutes and the mean operating room setup time was 45 minutes. The intraoperative complication rate was 15%, including conversion to laparotomy during attempted splenectomy to control bleeding at the splenic hilum in two and intraoperative percutaneous evacuation of a pneumothorax during Morgagni hernia repair in one. The conversions to laparotomy were reported to have occurred quickly.

The authors concluded that the 3-D visualization, articulating instruments, and motion scaling were the primary advantages of the robotic system. The primary disadvantages were the cost, training requirement, loss of tactile sensation, and additional operating room time required for system setup and docking. The authors detailed their technique with regard to patient positioning, port placement, and robotic cart positioning and docking and described their technique of elevating patients lighter than 20 kg off the operating table with foam padding. This enabled more lateral placement of the robotic instrument ports, thereby allowing the robotic arms and assistant surgeon greater mobility to pitch downward without encountering the operating table. We have used this technique and found it to be essential in smaller patients.

Lorincz et al. described seven patients who underwent robot-assisted procedures with the Zeus system.[139] They performed Nissen fundoplications in five children (three with gastrostomy), one cholecystectomy, and one Heller myotomy with partial fundoplication. Specifics regarding patient age and weight, as well as complications, were not included. However, the authors noted that their total procedure times and setup times decreased rapidly as their team gained experience with the robotic system. The first Nissen fundoplication took 4.5 hours, whereas their last took only 1.5 hours. They commented that tissue dissection and suture placement were accurate and knot tying secure.

Most recently, Knight et al. described 15 fundoplications with the Zeus system.[115] They performed 1 Heller myotomy with Dor fundoplication and 14 Nissen fundoplications and collected data regarding setup time, operating time, and outcomes. The mean patient age was 4.3 years (range, 2 months to 18 years) and the mean weight was 13 kg (range, 3.4 to 37.7 kg). Their mean operating time was 195 minutes, 323 minutes for the first case decreasing to 180 minutes for the last case. There were no postoperative complications.

Pediatric Urology

The use of robotic surgical systems in pediatric urology is gaining interest, with recent reports describing their use to perform complex reconstructive operations (see Table 4-4). Pedraza et al. reported the completion of a laparoscopic appendicovesicostomy (Mitrofanoff procedure) in a 7-year-old boy with the use of a four-port transperitoneal approach and the da Vinci system.[165] The total operative time was 6 hours, with no intraoperative or postoperative complications. The authors found the robotic system to be advantageous during the appendicovesical anastomosis. Similarly, the same group performed a robot-assisted laparoscopic bilateral heminephroureterectomy in a 4-year-old girl.[164] The total surgical time forthis procedure was 7 hours and 20 minutes, and no complications occurred. The authors suggested that the robotic interface facilitated dissection of the renal hilum and vessels and enabled the completion of a complex MAS operation.

In a review of robotics in pediatric urology, Peters describes the use of robot assistance (da Vinci system) to facilitate complex urologic procedures.[167] Although no case details are provided, the author describes the use of robotic assistance to perform a variety of cases, including

TABLE 4–4 Clinical Experience with Robotic Surgical Systems in Pediatric General Surgery

Author	Robotic System	Type of Study	Patient (*N*)	Operative Procedure	Results	Comments
Gutt et al.[79] and Heller et al.[88]	Da Vinci	Case series	14	11 fundoplication, 2 cholecystectomy, 1 bilateral salpingo-oophorectomy	Operative times: fundoplication, 146 min (mean); cholecystectomy, 105, 150 min; salpingo-oophorectomy, 95 min	No complications or conversion to laparotomy
Luebbe et al.[140]	Da Vinci	Case series	20	10 fundoplication, 3 cholecystectomy, 2 splenectomy, 1 urachus resection, 1 Morgagni diaphragmatic hernia, 3 biopsies, 1 lymphadenectomy	Mean times: OR setup, 45 min; patient preparation, 17 min; console operating time, 93 min (range, 10-299 min)	15% complications (2 conversions to laparotomy for bleeding, 1 pneumothorax)
Lorincz et al.[139]	Zeus	Case series	7	5 Nissen fundoplication, 1 cholecystectomy, 1 Hellermyotomy	Operative time for fundoplication reduced from 4.5 hr to 1.5 hr	Rapid improvement in case times as team progressed along learning curve
Knight et al.[115]	Zeus	Retrospective case review	15	14 Nissen fundoplication, 1 Heller myotomy with Dor fundoplication	Mean operating time, 195 min; 2 complications within first 30 days after surgery	Rapid improvement with learning; perceived benefit of greater ease and confidence in knot tying and suture placement
Pedraza et al.[165]	Da Vinci	Case report	1	Appendicovesicostomy (Mitrofanoff procedure)	Operative time, 6 hr; no complications	Robotic procedure useful during the appendicovesical anastomosis
Pedraza et al.[164]	Da Vinci	Case report	1	Bilateral heminephroureterectomy	Operative time, 7 hr, 20 min; no complications	Robotic interface facilitated dissection of the renal hilum and vessels
Peters[167]	Da Vinci	Review article	Not provided	Nephrectomies, pyeloplasties (both transperitoneal and retroperitoneal), antireflux procedures (transperitoneal and transvesical), appendicovesicostomy, redo megaureter, pyelolithotomy, and excision of a large müllerian remnant	Not provided	Transperitoneal approach more readily suited for current robotic systems
Le Bret et al.[128]	Zeus	Prospective clinical trial	56	Patent ductus arteriosus ligation (28 thoracoscopic, 28 robotic)	Operating room time: thoracoscopic, 83 min; robotic, 162 min Surgical procedure time: thoracoscopic, 24 min; robotic, 50 min	Longer operative time for robotic group; 1 conversion to videothoracoscopic; no significant difference in complications or outcome
Mihaljevic et al.[150]	Da Vinci	Case series	2	Vascular ring dissection	Total operative times: 172.5 min (mean) Robotic procedure times: 106.5 min (mean)	Total operative time longer than usually required for standard thoracoscopic procedure because of setup; dissection time slightly shorter in robotic cases

nephrectomy, pyeloplasty (both transperitoneal and retroperitoneal), procedures for vesicoureteral reflux (transperitoneal and transvesical), appendicovesicostomy, redo megaureter, pyelolithotomy, and excision of a large müllerian remnant. The author stated that although the robotic system can be used to perform retroperitoneal procedures, the transperitoneal approach is most readily used because of the size of the robotic instruments and arms and stressed the development of a dedicated team approach for efficient use of the robotic system.

Pediatric Cardiothoracic Surgery

At this time, only two reports have been published describing the use of robotic surgical systems in pediatric cardiothoracic surgery (see Table 4-4). Le Bret et al. reported a relatively large series of 56 children who underwent surgical closure of a patent ductus arteriosus.[128] The children were distributed into two groups, one group undergoing standard thoracoscopic repair and the other undergoing robot-assisted repair with the Zeus system. The authors did not detail their method of group assignment. Although the patient characteristics were generally similar, the robot-assisted group tended to consist of smaller and younger patients (mean age, 20 months; mean weight, 10.7 kg) than the standard thoracoscopy group did (mean age, 33 months; mean weight, 13.3 kg). No intraoperative complications occurred in either group. Twenty-seven of twenty-eight procedures allocated to the robot-assisted group were completed, with one patient requiring conversion to standard thoracoscopy because of failure to achieve adequate exposure. The total operating room and surgical procedure time was significantly longer for the robot-assisted group (mean total operating room time, 162 minutes; mean surgical procedure time, 50 minutes) than for the standard thoracoscopy group (mean total operating room time, 83 minutes; mean surgical procedure time, 24 minutes). These differences were statistically significant.

There were no significant differences in postoperative complications, intensive care unit stay, or hospital length of stay between the two groups. The authors concluded that although robot-assisted patent ductus arteriosus closure in small children was safe and feasible, it offered no advantages over standard thoracoscopy. Furthermore, they commented that the additional procedure time required for the robotic approach did not decline with experience and was therefore due to the complexity of the robot and not a learning curve.

In a more recent report, Mihaljevic et al. described use of the da Vinci system for the division of a vascular ring in two patients (ages 10 and 8 years, weighing 48 and 27 kg, respectively).[150] Total operating room times were 180 and 165 minutes with surgical procedure times of 115 and 98 minutes, respectively. The authors concluded that the enhanced visualization and increased dexterity provided by the robotic system represented significant advantages over standard thoracoscopy and highlighted the improved intracorporeal dexterity as an important feature that aided in the division of all fibrous bands around the trachea and esophagus. The authors stated that although the dissection time was slightly shorter in the robot-assisted cases than in standard thoracoscopy, the total operating room times were generally longer because of setup time.

Experimental Procedures

Although the published human experience has largely focused on relatively routine MAS procedures, several authors have reported the feasibility of performing more complex reconstructive operations in animal models. Hollands et al.,[96-98] Knight et al.,[115] and Lorincz et al.[139] have all described application of the Zeus system in a porcine model. Technically challenging procedures such as enteroenterostomy, hepaticojejunostomy, portoenterostomy, and esophagoesophagostomy were all demonstrated to be technically feasible (Table 4-5). Robot-assisted procedures and standard laparoscopic procedures had reasonably similar operating times and complication rates. In addition, survival studies indicate that the procedures are durable with reasonable long-term outcomes.

Similarly, Aaronson, Malhotra, Olsen, and their colleagues have described application of the da Vinci system in animal models to perform complex pediatric cardiovascular, neurosurgical, and urologic procedures,[1,143,161] including aortic anastomosis in juvenile lambs,[143] transvesical surgery,[161] and simulated myelomeningocele repair in a fetal lamb model.[1] In the latter study, the robotic system enabled the completion of laparoscopic, intrauterine repair of full-thickness skin lesions through small hysterostomies.[1]

Conclusion

At present, robotic surgical systems have been used in pediatric surgery primarily as a tool to facilitate MAS. The current published clinical experience with robotic pediatric surgery has been limited and consists largely of retrospective case reports and case series documenting feasibility and safety. On average, setup and operative times are longer with robotic cases than with standard laparoscopy. However, the rate of complications or conversion to open procedures has been low. At this time, significant long-term follow-up for any differences in clinical outcome has yet to be reported. Because the bulk of the published human experience represents relatively simple and routine MAS procedures, it may be some time before any significant clinical benefits are demonstrated.

In contrast to the human literature, published experimental series have demonstrated the feasibility and occasionally the efficacy of complex, reconstructive robot-assisted procedures in animal models. These applications represent the necessary future for robotic pediatric surgery inasmuch as the benefits of the robotic interface lie in their ability to facilitate fine dissection and intracorporeal suturing. Procedures such as repair of esophageal atresia, portoenterostomy, and ureteral reimplantation can all be performed today with existing laparoscopic equipment. However, mastery of these complex techniques in a MAS environment is extremely challenging. Robotic surgical systems have the potential to enable the completion of these technically challenging operations in a minimally invasive manner that retains the benefits of improved cosmesis, decreased postoperative pain, and potentially shorter hospital stay.

TABLE 4–5 Experimental Pediatric Robotic Procedures in Animal Models

Author	Operative Procedure	Robotic System	Type of Study	Procedure Times, Laparoscopic (mean)	Procedure Times, Robotic (mean)	Additional Results
Hollands et al.[96-98]	Porcine enteroenterostomy (5 laparoscopic, 5 robotic)	Zeus	Acute	Anesthesia, 176 min Operative time, 143 min Anastomotic time, 109 min	Anesthesia, 154 min Operative time, 139 min Anastomotic time, 93 min	All anastomoses were patent without narrowing; 1 small leak occurred in each group; no statistical differences
	Porcine hepaticojejunostomy (5 laparoscopic, 5 robotic)	Zeus	Acute	Anastomotic time, 66 min	Anastomotic time, 93 min	5 complications in the control group (3 leaks and 2 conversions); 1 complication in the robotic group (conversion)
	Porcine esophagoesophagostomy (5 laparoscopic, 5 robotic)	Zeus	Acute	Anesthesia time, 124 min Operative time, 97 min Anastomotic time, 89 min	Anesthesia time, 151 min Operative time, 131 min Anastomotic time, 125 min	All anastomoses were patent with no stricture; 1 anastomosis had a small leak; no statistically significant differences
	Porcine portoenterostomy (10 laparoscopic, 10 robotic)	Zeus	Acute	Anesthesia time, 125 min Operative time, 98 min Anastomotic time, 60 min	Anesthesia time, 164 min Operative time, 137 min Anastomotic time, 94 min	3 complications in the control group (1 narrowed anastomosis and 3 disrupted anastomoses); 4 complications in the robotic group (1 leak, 1 narrowed anastomosis, 2 disrupted anastomoses)
Lorincz et al.[139]	Porcine portoenterostomy (8 robotic)	Zeus	Survival (1 mo)	N/A	Total operative time, 380 min Setup time, 20 min End-to-side anastomosis, 129 min Biliary tract dissection, 36 min Portoenterostomy, 96 min	5/8 animals survived >1 mo postop; all lab values normal; no anastomotic stenoses and the anastomoses were well healed
	Porcine esophagoesophagostomy (7 robotic)	Zeus	Survival (1 mo)	N/A	Mean operative time, 120 min	5/8 animals survived to 1 mo postop; all required 1-2 postop dilatations; postmortem showed well-healed anastomoses
Malhotra et al.[143]	Juvenile ovine thoracic aortic anastomosis (5 robotic)	Da Vinci	Survival (6-12 hr)	N/A	Aortic clamp time, 47 min Anastomotic time, 26 min	All 5 lambs survived the procedure; mean anastomotic burst pressure, 163 ± 9 mm Hg
Aaronson et al.[1]	Intrauterine fetal ovine simulated myelomeningocele repair (6 robotic)	Da Vinci	Survival (7-11 days)	N/A	In utero procedure time, steep learning curve from just under 120 min to just over 30 min within 6 cases	4/6 lambs survived until sacrifice; intrauterine endoscopic surgery is feasible
Olsen et al.[161]	Porcine Cohen cross-trigonal ureter reimplantations (14 robotic reimplantations)	Da Vinci	Survival	N/A	Mean operative time, 68 min	Postop evaluation showed resolution of vesicoureteral reflux

The two systems currently in use offer many of the same advantages over standard MAS techniques: 3-D visualization, articulated instrumentation, intuitive movement, tremor reduction, and motion scaling., In addition, they share many of the same limitations that restrict their widespread adoption in pediatric surgery: high initial and recurring cost, relatively limited instrument selection, necessity for dedicated training, significant setup time, and lack of haptic feedback. In particular, the large system size and instrument dimensions relative to pediatric patients are main issues that must be resolved for robotic pediatric surgery to further develop. However, authors have generally applauded the technologic features of the robotic systems.[50,128,140] Although quantitative clinical value has not yet been demonstrated, most authors have subjectively concluded that the robotic systems appear to enhance surgical precision and make complex MAS procedures easier to perform. Further studies are therefore warranted to fully evaluate the potential benefits and application of robotic surgery to the pediatric population.

The advent of MAS has brought with it a wealth of potential benefits for the patient. However, the inherent limitations of operating in a laparoscopic setting pose significant challenges for the surgeon, and this is only magnified as procedures become more complex, such as those encountered in pediatric surgery. The incorporation of robotic and computer technology has the potential to contribute significantly to the advancement of this area. As the technology continues to be refined, its ultimate acceptance will demand that the issues of cost, training, size, safety, efficacy, and clinical utility all be addressed.

MICROTECHNOLOGIES AND NANOTECHNOLOGIES—SIZE MATTERS

An arsenal of technology will emerge from material science and its application principles to microelectromechanical (MEMS)[211] and nanoelectromechanical (NEMS) systems. Just as the electronics industry was transformed by the ability to manipulate the electronic properties of silicon, manipulation of biomaterials on a similar scale is now possible. For the last 40 years the common materials of stainless steel, polypropylene, polyester, and polytetrafluoroethylene have been unchanged. A recent example of this potential is the use of nitinol (equiatomic nickel-titanium), a metal alloy with the property of shape memory.

An important concept as well as distinction in device manufacturing is that of "top down" versus "bottom up" assembly. Top down refers to the concept of starting with a raw material and shaping it into a device. In a typical MEMS device, silicon is etched, heated, and manipulated to its final form. In the nascent field of nanotechnology, the underlying conceptual principle is that of self-assembly. Here, component ingredients are placed together under optimal conditions and self-assemble into materials. This process is much more one of biologic assembly.

Microelectromechanical Systems

The evolution of surgical technology has followed the trends that are set by most industries—the use of technology that is smaller, more efficient, and more powerful. This trend, which has application in the medical and surgical world, is embodied in MEMS devices.[179]

Most MEMS devices are less than the size of a human hair, and although they are scaled on the micron level, they may be used singly or in groups. MEMS devices have been used for years in automobile airbag systems and in inkjet printers.

Because the medical community relies increasingly on computers to enhance treatment plans, it requires instruments that are functional and diagnostic. Such a level of efficiency lies at the heart of MEMS design technology, which is based on creating devices that can actuate, sense, and modify the outside world on the micron scale. The basic design and fabrication of most MEMS devices resemble the fabrication of a standard integrated circuit, which includes crystal growth, patterning, and etching.[188]

Devices and Examples

MEMS devices have particular usefulness in biologic applications because of their small volume, low energy, and nominal force.[65] Increased efficacy of instrumentation and new areas of application are also emerging from biomedical applications of MEMS systems. There are two basic types of MEMS devices: sensors and actuators. Sensors transduce one type of energy (such as mechanical, optical, thermal, or otherwise) into electrical energy or signals. Actuators take energy and transform it into an action.

Sensors

Sensors transduce or transform energy into an electrical signal. The incoming energy may be mechanical, thermal, optical, or magnetic. Sensors may be active or passive systems. Active sensors derive their own energy from an input signal, whereas passive sensors require an outside energy source to function. Almost all these devices are in their developmental stage, but give form to the concept.

Data Knife and H-Probe Surgical Instruments: MEMS devices are particularly suited to surgical applications because their small dimensions naturally integrate onto the tips of surgical tools. One example is the "Data Knife" (Verimetra, Inc., Pittsburgh), which uses microfabricated pressure sensors attached to the blade of a scalpel (Fig. 4-13). While cutting, the Data Knife pressure sensors cross-reference with previously gathered ex vivo data to inform the surgeon about the type of tissue that is

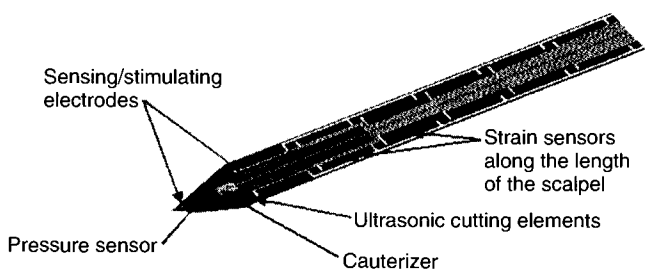


Figure 4-13 Data Knife microelectromechanical-based scalpel. (Courtesy of Verimetra, Inc., Pittsburgh.)

being divided. This information becomes particularly useful during endoscopic cases in which a sense of tactile feedback is reduced or lost entirely.

Verimetra's H-probe uses similar sensors to "palpate" calcified plaque transmurally during coronary bypass surgery. The intention is to eliminate poor positioning of the bypass graft conduit by more precisely targeting an ideal anastomotic site before arteriotomy.

Arterial Blood Gas Analyzer: MEMS technology can be applied to the analysis of arterial blood gas. This MEMS-based analyzer was founded on established methods in infrared spectroscopy. It consists of an infrared light source, an infrared sensor, and an optical filter. The infrared light is passed through the filter, which is designed to monitor the infrared spectra of oxygen, carbon dioxide, and other associated blood gases. Because most gases have a known infrared absorption, the sensor can be designed with specific values for infrared signatures.

Once again, because of microscaling techniques and the relatively small sample size, the test can be performed in less time than needed for conventional arterial blood gas analysis. One specific example is an arterial blood gas catheter for monitoring blood in preterm infants, in which real-time data can be gathered by way of oxygen- and carbon dioxide–specific sensors.

Blood Pressure Sensor: The biggest success story in medical MEMS technology is the disposable blood pressure sensor. Disposable blood pressure sensors replace reusable silicon beam or quartz capacitive pressure transducers, which can cost as much as $600 and have to be sterilized and recalibrated for reuse. These expensive devices measure blood pressure with a saline solution–filled tube-and-diaphragm arrangement that must be connected directly to the arterial lumen. In the silicon MEMS blood pressure transducer, pressure corresponds to deflection of a micromachined diaphragm. A resistive element, a strain gauge, is ion-implanted on the thin silicon diaphragm. The piezoresistor changes output voltage with variations in pressure. Temperature compensation and calibration can be integrated in one sensor.

Other Microelectromechanical Sensors in Medicine: The Wheatstone bridge piezoresistive silicon pressure sensor is a prime example of a MEMS device that is used commonly in medical applications. Able to measure pressures that range from less than 0.1 to more than 10,000 psi, this sensor combines resistors and an etched diaphragm structure to provide an electrical signal that changes with pressure. Primarily, these types of sensors are used in blood pressure monitoring equipment, but their use in the medical field extends far beyond that. These types of sensors can be found in respiratory monitors, dialysis machines, infusion pumps, and medical drilling equipment. They are also used in inflatable hospital bed mattresses or to signal an alarm on detection of lack of motion over a significant time frame in apnea monitors.

Actuators

An actuator is a fluid-powered or electrically powered device that supplies force and motion. Several kinds of actuators are used in MEMS devices, including electrostatic, piezoelectric, thermal, magnetic, and phase recovery. Actuators in medicine are used in valves, accelerometers, and drug delivery systems. Future use to produce muscle activation or "artificial muscles" is predicted.

Drug Delivery Systems: MEMS devices are used in drug delivery systems in the form of micropumps.[126] A typical drug pump consists of a pump chamber, an inlet valve, an outlet valve, a deformable diaphragm, and an electrode. When a charge is applied to the electrode, the diaphragm deforms, which increases the volume in the pump chamber. The change in volume induces a decrease in pressure in the pump chamber. This decreased pressure opens the inlet valve. When the charge is terminated, the pressure returns to normal by closing the inlet valve, opening the outlet valve, and allowing the fluid to exit.

Other micropumps incorporate pistons or pressurized gas to open the outlet valves. One of the more attractive applications for implantable pumps is insulin delivery.

Current insulin micropumps have disadvantages, most notably their expense. The drug supply must be refilled once every 3 months, and each pump costs between $10,000 and $12,000. Furthermore, insulin is unstable at core body temperature. Therefore, an insulin analogue must be synthesized that would be stable at physiologic temperatures. Thinking forward, a biomechanical pancreas that senses glucose and insulin levels and titrates insulin delivery would be an interesting MEMS combination of a sensor and an actuator.

Next Steps

MEMS devices are in the same state today as the semiconductor industry was in the 1960s. Like the first semiconductors, MEMS devices are now largely funded by government agencies such as the Defense Advance Research Projects Agency. Relatively few commercial companies have taken on MEMS devices as a principal product. However, no one could have predicted in 1960 that 40 years later, a semiconductor would be on virtually every desktop in the United States. It is then not unreasonable to predict potential value, including surgical applications, for MEMS devices. Indwelling microsensors for hormone and peptide growth factors might replace episodic examinations, laboratory determinations, or CT scans to monitor tumor recurrence. As more devices are fabricated, the design process becomes easier, and the next technology can be based on what was learned from the last. At some point in the future when more affordable technology becomes available,[179] we will "see" MEMS devices as common surgical modalities, smart instruments, in-line laboratories, surveillance devices, and perhaps, cellular or even DNA insertion.

Nanoelectromechanical Systems

Applications of nanotechnology and NEMS systems in medicine and surgery have recently been reviewed.[68] Size does matter. In medicine and biology the major advantage of decreasing the size scale is the ability to enable materials or particles to find places in body compartments

to which they could otherwise not be delivered. Current and future applications of surgical interest include coating and surface manipulation, the self-assembly or biomimicry of existing biologic systems, and targeted therapy in oncology.

Coating and Surface Manipulation

Although most medical devices are composed of a bulk material, biologic incorporation or interaction occurs only at the thinnest of surfaces. To optimize this surface interaction, sintered orthopedic biomaterials have been developed. A thin layer of beads is welded or "sintered" via heat treatment on top of the bulk material.[169] This bead layer optimizes bone ingrowth, whereas the bulk material is responsible for mechanical stability of the device. Hydroxyapatite-coated implants represent a biologic advance in which the device is coated with ceramic hydroxyapatite,[13] thereby inducing bony ingrowth by mimicking (biomimicry) the crystalline nature of bone. Future attempts involve coating with the RGD peptide, the major cell attachment site in many structural proteins.

Cardiovascular stents, and now drug-eluting stents, provide a similar example. The current generation of drug-eluting stents has a micron-thick coating made of a single polymer that releases a drug beginning at the time of implantation.[99] The drug coating of rapamycin or paclitaxel diffuses slowly into the tissue microenvironment to prevent a fibrotic reaction. The future ideal stent will probably be engineered to optimize the bulk material and the coating. Indeed, the perfectly biocompatible material may be one in which the bulk material is artificial and the surface is seeded with the patient's own cells, for example, an endothelialized Gore-Tex vascular stent.[159]

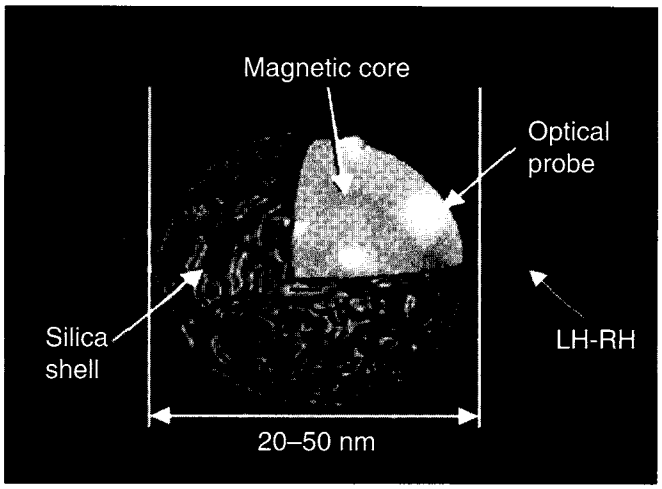
Self-Assembly

NEMS materials are produced from a self-directed or self-assembly process in which mixtures of materials are allowed to condense into particles, materials, or composites.[126] Thus, NEMS processing starts with a nonsolid phase, typically a solution, and by manipulating the environment, materials are created.

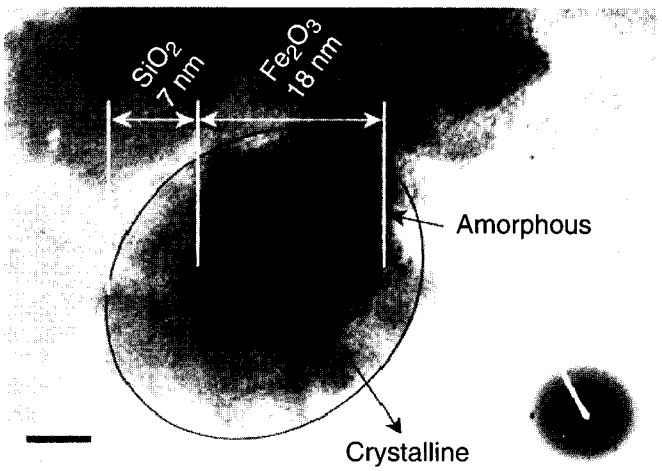
Recently, biologic molecules, including proteins and DNA, have been used to stabilize nanoparticle crystals and create materials with unique properties, thus opening the door to unlimited diversity in the next generation of nanoparticles and materials.[144,194] Such processes mimic nature's ability to produce materials such as pearls, coral, and collagen.

Oncology

More than in any other field, microscale and nanoscale technologies will provide the field of oncology with critical therapeutic advances. In considering the perverse biologic process of malignant transformation and spread, our current therapies are gross and nontargeted. Figure 4-14 depicts a complex nanoparticle[84] composed of an iron oxide core surrounded by silicon oxide shells. Ligands may be attached to the silicon oxide coating, which may then target the iron oxide to a specific site. Such technology can be used for diagnostic purposes based on tumor permeability or for therapeutic options, or for both.



A



B

Figure 4-14 Schematic of a nanoparticle. An iron oxide core is surrounded by a silicon oxide shelf. Ligands attached to the silicon oxide can target the iron oxide to a specific site or potentially a tumor. The iron oxide can be heated in a magnetic field. Alternatively, the iron oxide may carry a toxin, a gene, or a pharmaceutical.

Harisinghani et al.[84] used iron oxide nanoparticles to identify tumor metastases in lymph nodes in patients with prostate cancer. The authors demonstrated increased sensitivity and specificity in identifying lymph nodes that ultimately contained tumor. Further work with magnetic nanoparticles functionalized with tumor-specific antibodies will enhance specific uptake by tumors.

SURGICAL SIMULATION AND VIRTUAL REALITY

Simulation and virtual reality (VR)[71,146] are two concepts that may reshape the way we think about surgical education, rehearsal, and practice. The practice of surgery is a visual, cognitive, and manual art and science that

requires the physician to process increasingly large amounts of information. Techniques are becoming more specific and complex, and decisions are often made with great speed and under urgent circumstances, even when rare problems are being dealt with.

Surgical Simulation

Simulation is a device or exercise that enables the participant to reproduce or represent, under test conditions, phenomena that are likely to occur in actual performance. There must be sufficient realism to suspend the disbelief of the participant. Simulation is firmly established in the commercial airline business as the most cost-effective method of training pilots. Pilots must achieve a certain level of proficiency in the simulator before they are allowed to fly a particular aircraft and must pass regular proficiency testing in the simulator to keep their license. Military organizations use a similar method for training in basic flying skills and find simulation useful in teaching combat skills in complex tactical situations. Surgical simulation therefore has roots in the techniques and experiences that have been validated in other high-performance, high-risk organizations.

The expense and risk of learning to fly motivated Edward Link to construct a mechanical device that he called "the pilot maker" (Link, *http://www.link.com/history.html*). The addition of instrument sophistication enables the training of individuals to fly in bad weather. At the onset of World War II, with an unprecedented demand for pilot trainees, tens of thousands were trained in Link simulators.[89]

The medical community is beginning to use simulation in several areas for training medical personnel, notably surgeons, anesthesiologists, phlebotomists, paramedics, and nurses. The ability of the simulator to drill rehearsed pattern recognition repetitively in clinical practice makes just as much sense for the surgical disciplines as it does for aviators.

Surgical care entails a human risk factor that is related to both the underlying disease and the therapeutic modality. Risk can be reduced through training. One of the ways to accomplish both these goals is through simulation.

Simulation is loosely defined as the act of assuming the outward qualities or appearances of a given object or series of processes.[181] It is commonly assumed that simulation will be coupled with a computer, but this is not requisite. Simulation is a technique (not a technology) used to replace or amplify real experiences with guided experience that involves substantial aspects of the real world in a fully interactive manner.[64] To perform a simulation, it is only necessary to involve the user in a task or environment that is sufficiently "immersive" that the user is able to suspend reality to learn or visualize a surgical teaching point. The knowledge that is gained is then put to use in education or in the live performance of a similar task. Surgeons can learn to tie knots with a Linux-based computer or simulate the actions of a laparoscopic appendectomy with the use of a cardboard box painted to resemble a draped abdomen.

Visual Display Systems in Simulation

Simulator technology involves the design of training systems that are safe, efficient, and effective for orienting new trainees or providing advanced training to established clinicians. This involves teaching specific skills and generating scenarios for the simulation of critical or emergency situations. The entertainment industry is by far the main user and developer of visual displays. So much headway has been made in the advancement of visual technologies by the entertainment industry that many visual devices used in simulation are borrowed from these foundations. Considering that the graphic computing power of a $100,000 supercomputer in 1990 was essentially matched by the graphic capability of a $150.00 video game system in 1998, the available technology today is more than capable of representing a useful surgical simulation faithfully.[232]

Props are a key component of the visual act of simulation. Although laparoscopic surgical procedures can be represented on a desktop computer, a much more immersive experience can be carried out by involving monitors and the equipment used in an actual operating room. As an example, mannequin simulators, though internally complex, can serve to complement the simulation environment. Simulation of procedures such as laparoscopic surgical procedures should use displays similar to those present in the actual operating room.

Simulation of open procedures, on the other hand, requires systems that are presently in the developmental stage. The level of interaction between the surgeon and the simulated patient requires an immersive display system such as a head-mounted display (HMD). The best approach for a developer of a simulator for open procedures would be to choose a system with good optical qualities and concentrate on developing a clear, stable image. Designs for this type of visualization include "see-through displays" in which a synthetic image is superimposed on an actual model.[186] These systems use a high-resolution monitor screen at the level of the operating table because the characteristics of the displayed image must be defined in great detail.

Human/Simulator Interface and Tactile Feedback

Force feedback is the simulation of weight or resistance in a virtual world.[106] Tactile feedback is the perception of a sensation applied to the skin, typically in response to contact. Both tactile feedback and force feedback were necessary developments because the user needs the sensation of touching the involved virtual objects. This so-called *haptic loop*, or human-device interface, was originally developed with remote surgical procedures in mind and has much to offer the evolution of surgical simulation.

Technologies that address haptic feedback are maturing, nurtured by the rapid development of haptic design industries in the United States, Europe, and Japan and in many university-based centers.[106] Haptic technologies have been used in simulations of laparoscopic surgical procedures; however, extending this technology to open

procedures in which a surgeon can, at will, select various instruments will require a critical innovation.

Image Generation

The generation of 3-D, interactive graphic images of a surgical field is the next level in surgical simulation. Seeing and manipulating an object in the real world are different from manipulating the same object in virtual space. Most objects that are modeled for simulations are assumed to be solids. In human tissue, with the possible exception of bone, such is not the case. Many organs are deformable semisolids, with potential spaces. Virtual objects must mirror the characteristics of objects in the real world. Even with today's computing power, the task of creating a workable surgical surface (whether skin, organ, or vessel) is extremely difficult.

A major challenge in the creation of interactive surgical objects is the reality that surgeons change the structural aspects of the field through dissection. On a simulator, performing an incision or excising a lesion produces such drastic changes that the computer program supporting the simulation is frequently incapable of handling such complexity. This still does not include the issue of blood flow, which would cause additional changes in the appearance of the simulated organ. Furthermore, the simulation would have to be represented in real time, which means that changes must appear instantaneously.

To be physically realistic, simulated surgical surfaces and internal organs must be compressible in response to pressure applied on the surface, either bluntly or by incision. Several methods of creating deformable, compressible objects exist in computer graphic design.

Frequently, simulator graphic design is based on voxel graphics. A voxel is an approximation of volume, much in the same way a pixel is an approximation of area. Imagine a voxel as a cube in space, with length, width, and depth. Just as pixels have a fixed length and width, voxels have a fixed length, width, and depth. The use of volume as the sole modality to define a "deformable object," however, does not incorporate the physics of pressure, stress, or strain. Therefore, the graphic image will not reflect an accurate response to manipulation. The voxel method does not provide a realistic representation of the real-time changes in an organ's architecture that would occur after a simulated incision.

A more distinct approach to the solution of this problem is provided by the use of finite elements. Finite elements allow the programmer to use volume, pressure, stress, strain, and density as bulk variables. This creates a more detailed image that can be manipulated through blunt pressure or incision. Real-time topologic changes are also supported.

For the moment, a good alternative solution to the problem is to avoid computational models. Some groups have used hollow mannequins with instruments linked to tracking devices that record position. Task trainers allow one to practice laparoscopic skills directly by use of the equivalent of a cardboard box with ports to insert endoscopic tools. These tools are used to complete certain tasks, such as knot tying or object manipulation.

Simulation in Education, Training, and Practice

Historically, surgical training has been likened to an apprenticeship. Residents learn by participating and taking more active roles in patient care or the operative procedure as their experience increases. Despite potential flaws, this model has successfully trained generations of surgeons throughout the world. Error and risk to patients are inherent in this traditional method of education despite honest attempts at mitigation and will always be a factor in the field of surgery, no matter how it is taught. There are new methods of surgical training, however, that can help reduce error and risk to the patient.[155,189]

Training in simulated environments has many advantages. The first advantage is truly the crux of simulation: it provides an environment for consequence-free error, or freedom to fail. Simulator-based training incurs no real harm, injury, or death to the virtual patient. If a student transects the common duct during a simulated cholecystectomy, the student simply notes the technical error and learns from the mistake. Furthermore, simulations can be self-directed and led by a computer instructor or can be monitored and proctored by a real instructor, which means that students can learn on their own time, outside the operating room.[187]

Simulators are pliable tools. Depending on the assessment goals of a particular simulator, tasks can be modified to suit the educational target. For example, self-contained "box trainers" that are used to teach a particular dexterous skill can be modified to be less or more difficult or to teach grasping skills versus tying skills. In more complex computer-based simulations, variables can be changed automatically by the computer or manually by the instructor, even during the simulation. These variables range from changes in the graphic overlay to the introduction of an unexpected medical emergency. Approaches to learning laparoscopic navigational skills within the human body have benefited considerably from such techniques. A prime objective of surgical education is to learn how to function mentally and dexterously in a 3-D environment. Surgical "fly-through" programs can be invaluable resources to learn this kind of special orientation inside the human body.[37]

Perhaps one of the greatest benefits of surgical simulation is the ability of early learners to become skilled in basic tasks that have not previously been presented in formal training. The orientation of medical students, now frequently excluded from patient care tasks, may aid in their engagement, education, and recruitment to surgical careers. Therefore, the most consistent success has been the discovery that simulators are most beneficial to individuals with little or no previous experience in the simulated task.[170]

Looking Forward

Simulation success, particularly in the aviation industry, strongly suggests utility to medical and surgical applications. As with any form of new technology, advances depend on many factors. A product made solely for the