PEDIATRIC SURGERY

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SEVENTH EDITION

VOLUME ONE

EDITOR IN CHIEF

Arnold G. Coran, MD

Emeritus Professor of Surgery
Section of Pediatric Surgery
University of Michigan Medical School and
C. S. Mott Children's Hospital
Ann Arbor, Michigan
Professor of Surgery
Division of Pediatric Surgery
New York University Medical School
New York, New York

ASSOCIATE EDITORS

N. Scott Adzick, MD

Surgeon-in-Chief
The Children's Hospital of Philadelphia
C. Everett Koop Professor of Pediatric Surgery
University of Pennsylvania School of Medicine
Philadelphia, Pennsylvania

Thomas M. Krummel, MD

Emile Holman Professor and Chair
Department of Surgery
Stanford University School of Medicine
Susan B. Ford Surgeon-in-Chief
Lucile Packard Children's Hospital
Stanford, California

Jean-Martin Laberge, MD

Professor of Surgery
McGill University
Attending Pediatric Surgeon
Montreal Children's Hospital of the McGill University
Health Centre
Montreal, Quebec, Canada

Robert C. Shamberger, MD

Chief of Surgery
Children's Hospital Boston
Robert E. Gross Professor of Surgery
Harvard Medical School
Boston, Massachusetts

Anthony A. Caldamone, MD

Professor of Surgery (Urology) and Pediatrics
Brown University School of Medicine
Chief of Pediatric Urology
Hasbro Children's Hospital
Providence, Rhode Island

EMERITUS EDITORS

Jay L. Grosfeld, MD

Lafayette Page Professor of Pediatric
Surgery and Chair, Emeritus
Section of Pediatric Surgery
Indiana University School of Medicine
Surgeon-in-Chief, Emeritus
Pediatric Surgery
Riley Children's Hospital
Indianapolis, Indiana

James A. O'Neill, Jr., MD

J. C. Foshee Distinguished Professor
and Chairman, Emeritus
Section of Surgical Sciences
Vanderbilt University School of
Medicine
Nashville, Tennessee

Eric W. Fonkalsrud, MD

Emeritus Professor of Surgery and
Chief of Pediatric Surgery
University of California, Los Angeles
Los Angeles, California

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1600 John F. Kennedy Blvd.
Ste 1800
Philadelphia, PA 19103–2899

PEDIATRIC SURGERY

ISBN: 978-0-323-07255-7
Volume 1 9996085473
Volume 2 9996085538

Library of Congress Cataloging-in-Publication Data

Pediatric surgery. —7th ed. / editor in chief, Arnold G. Coran ; associate editors, N. Scott Adzick . . . [et al.].
p. ; cm.
Includes bibliographical references and index.
ISBN 978-0-323-07255-7 (2 vol. set : hardcover : alk. paper)
I. Coran, Arnold G., 1938- II. Adzick, N. Scott.
[DNLM: 1. Surgical Procedures, Operative. 2. Child. 3. Infant. WO 925]

617.9'8—dc23

2011045740

Editor: Judith Fletcher
Developmental Editor: Lisa Barnes
Publishing Services Manager: Patricia Tannian
Senior Project Manager: Claire Kramer
Designer: Ellen Zanolle

Printed in the United States of America

Last digit is the print number: 9 8 7 6 5 4 3 2

About the Editors

ARNOLD G. CORAN, MD, is Emeritus Professor of Surgery at the C. S. Mott Children's Hospital and the University of Michigan Medical School. He was the Chief of Pediatric Surgery and the Surgeon-in-Chief at the C. S. Mott Children's Hospital and Professor of Pediatric Surgery at the University of Michigan Medical School from 1974 to 2006. He is also currently Professor of Surgery in the Division of Pediatric Surgery at New York University School of Medicine. He was one of the editors of the fifth and sixth editions of *Pediatric Surgery* and is the current Editor in Chief of this seventh edition. His expertise in pediatric surgery centers on complex esophageal and colorectal diseases in infants and children. He is the past President of the American Pediatric Surgical Association and the past Chairman of the Surgical Section of the American Academy of Pediatrics. He has been married to Susan Coran for 50 years and has three children and nine grandchildren.

N. SCOTT ADZICK, MD, has served as the Surgeon-in-Chief and Director of The Center for Fetal Diagnosis and Treatment at The Children's Hospital of Philadelphia since 1995. He is the C. Everett Koop Professor of Pediatric Surgery at the University of Pennsylvania School of Medicine. Dr. Adzick was raised in St. Louis, received his undergraduate and medical degrees from Harvard, and has a Master of Medical Management degree from Carnegie Mellon University. He was a surgical resident at the Massachusetts General Hospital and a pediatric surgery fellow at Boston Children's Hospital. His pediatric surgical expertise is centered on neonatal general and thoracic surgery, with a particular focus on clinical applications of fetal diagnosis and therapy. He has received grant support from the National Institutes of Health for more than 20 years and has authored more than 550 publications. He was elected to the Institute of Medicine of the National Academy of Science in 1998. Scott and Sandy Adzick have one son.

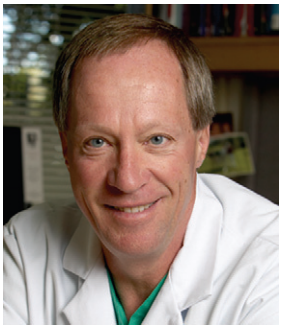
ANTHONY A. CALDAMONE, MD, graduated from Brown University and Brown School of Medicine. He was the first graduate of the medical school to become full professor at the institution. He did his residency at the University of Rochester and completed his fellowship under Dr. John W. Duckett at The Children's Hospital of Philadelphia. He is currently Professor of Surgery (Urology) and Pediatrics and Program Director for the Urology Residency at Brown University School of Medicine and Chief of Pediatric Urology at Hasbro Children's Hospital in Providence.

Dr. Caldamone has served as President of the New England Section of the American Urological Association (AUA). He has also served as Secretary-Treasurer and President of the Society for Pediatric Urology. He has been on several committees of the AUA including the Socio-Economic Committee, Publications Committee, and Nominating Committee. He is currently Executive Secretary of the Pediatric Urology Advisory Council. Locally he has served as President of the Rhode Island Urological Society, as President of the Brown Medical Alumni Association, as Chairman of the Board of Directors of Komedyplast Foundation, and as a member of the Board of Regents of La Salle Academy.

Dr. Caldamone has been on several medical missions to the Middle East, South America, and Bangladesh and has been on the Board of Directors of Physicians for Peace.

He was one of the editors of the sixth edition of *Pediatric Surgery.* He is currently an Editor for the *Journal of Pediatric Urology* and is Editor in Chief of the *Dialogues in Pediatric Urology.*

Dr. Caldamone is married to Barbara Caldamone and has two children, Amy and Matthew.



THOMAS M. KRUMMEL, MD, is the Emile Holman Professor and Chair of the Department of Surgery at Stanford University and the Susan B. Ford Surgeon-in-Chief at Lucile Packard Children's Hospital. Dr. Krummel has served in leadership positions in the American College of Surgeons, the American Pediatric Surgical Association, the American Surgical Association, the American Board of Surgery, and the American Board of Pediatric Surgery. He has mentored more than 150 students, residents, and postdoctoral scholars. He and his wife, Susie, have three children.

JEAN-MARTIN LABERGE, MD, is Professor of Surgery at McGill University and surgeon at the Montreal Children's Hospital of the McGill University Health Centre. He was the Director of Pediatric Surgery at the Montreal Children's Hospital from 1996 to 2008 and Program Director from 1994 to 2008. He is editorial consultant for the *Journal of Pediatric Surgery* and *Pediatric Surgery International* and was guest editor of two issues of *Seminars in Pediatric Surgery.* He has contributed chapters to several textbooks, including previous editions of *Pediatric Surgery,* Holcomb and Murphy's *Ashcraft's Pediatric Surgery,* Taussig and Landau's *Pediatric Respiratory Medicine,* and *Paediatric Surgery: A Comprehensive Text for Africa.* His research has focused on the effects of fetal tracheal occlusion to promote lung growth. His clinical interests include fetal diagnosis and treatment, congenital lung lesions, and anorectal malformations. He was President of the International Fetal Medicine and Surgery Society and is the immediate past President of the Canadian Association of Paediatric Surgeons (2009–2011). He has been married to Louise Caouette-Laberge, a pediatric plastic surgeon, for 34 years and has four children and three grandchildren.

ROBERT C. SHAMBERGER, MD, is the Robert E. Gross Professor of Surgery at Harvard Medical School and is Chief of Surgery at Children's Hospital in Boston.

Dr. Shamberger's expertise in pediatric surgery centers on oncology, inflammatory bowel disease, and chest wall deformities. He was Chair of the Surgical Committee for the Pediatric Oncology Group and Children's Oncology Group, as well as a member of the National Wilms' Tumor Study Group. He is the current President of the American Pediatric Surgical Association and Chairman of the Section on Surgery of the American Academy of Pediatrics. He has been married to Kathy Shamberger for 39 years and has three children and one grandchild.

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, Tennesee

Obinna O. Adibe, MD
Assistant Professor of Surgery
Assistant Professor in Pediatrics
Duke University School of Medicine
Durham, North Carolina

Jeremy Adler, MD, MSc
Assistant Professor
Pediatrics and Communicable Diseases
University of Michigan
C. S. Mott Children's Hospital
Ann Arbor, Michigan

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

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

Walter S. Andrews, MD
Professor of Pediatric Surgery
Department of Surgery
University of Missouri at Kansas City
Director of Renal Liver Intestinal Pediatric Transplantation Programs
Department of General Surgery
Children's Mercy Hospital
Kansas City, Missouri

Harry Applebaum, MD
Attending Pediatric Surgeon
Southern California Permanente Medical Group
Clinical Professor of Surgery
David Geffen School of Medicine
University of California, Los Angeles
Los Angeles, California

Marjorie J. Arca, MD
Associate Professor
Division of Pediatric Surgery
Medical College of Wisconsin
Clinical Director
Pediatric Surgical Critical Care
Children's Hospital of Wisconsin
Milwaukee, Wisconsin

Daniel C. Aronson, MD, PhD
President
International Society of Paediatric Surgical Oncology
Department of Surgery/Pediatric Surgery
Radboud University Nijmegen Medical Center
Nijmegen, The Netherlands

Richard G. Azizkhan, MD, PhD
Surgeon-in-Chief
Lester Martin Chair of Pediatric Surgery
Pediatric Surgical Services
Cincinnati Children's Hospital Medical Center
Professor of Surgery and Pediatrics
University of Cincinnati College of Medicine
Cincinnati, Ohio

Robert Baird, MD CM, MSc, FRCSC
Assistant Professor of Surgery
Pediatric General Surgery
Montreal Children's Hospital
McGill University
Montreal, Quebec, Canada

Sean Barnett, MD, MS
Assistant Professor of Surgery
Division of Pediatric General and Thoracic Surgery
Cincinnati Children's Hospital Medical Center
Cincinnati, Ohio

Douglas C. Barnhart, MD, MSPH
Associate Professor
Department of Surgery and Pediatrics
University of Utah
Attending Surgeon
Primary Children's Medical Center
Salt Lake City, Utah

Katherine A. Barsness, MD
Assistant Professor of Surgery
Division of Pediatric Surgery
Northwestern University
Feinberg School of Medicine
Attending Physician
Division of Pediatric Surgery
Children's Memorial Hospital
Chicago, Illinois

Robert H. Bartlett, MD
Professor Emeritus of Surgery
University of Michigan Medical School
Ann Arbor, Michigan

Laurence S. Baskin, MD
Professor and Chief, Pediatric Urology
Departments of Urology and Pediatrics
University of California, San Francisco
San Francisco, California

Spencer W. Beasley, MB ChB, MS, FRACS
Professor and Clinical Director
Department of Pediatric Surgery
Christchurch Hospital
Professor
Department of Surgery
Christchurch School of Medicine and Health Sciences
University of Otago
Christchurch, New Zealand

Michael L. Bentz, MD
Professor and Chairman
University of Wisconsin Plastic Surgery
University of Wisconsin-Madison
Madison, Wisconsin

Deborah F. Billmire, MD
Professor
Department of Surgery
Section of Pediatric Surgery
Indiana University
Indianapolis, Indiana

Scott C. Boulanger, MD, PhD
Assistant Professor of Surgery
Division of Pediatric Surgery
Case Western Reserve University School of Medicine
Cleveland, Ohio

Mary L. Brandt, MD
Professor and Vice Chair
Michael E. DeBakey Department of Surgery
Baylor College of Medicine
Houston, Texas

John W. Brock III, MD
Professor and Director
Division of Pediatric Urology
Vanderbilt University
Surgeon-in-Chief
Monroe Carell Jr. Children's Hospital at Vanderbilt
Nashville, Tennesee

Rebeccah L. Brown, MD
Associate Professor of Clincal Surgery and Pediatrics
Department of Pediatric Surgery
Cincinnati Children's Hospital Medical Center
Associate Director of Trauma Services
Department of Trauma Services
Associate Professor of Surgery
Department of Surgery
University of Cincinnati Hospital
Cincinnati, Ohio

Imad F. Btaiche, PhD, BCNSP
Clinical Associate Professor
Department of Clinical Social and Administrative Sciences
University of Michigan College of Pharmacy
Clinical Pharmacist, Surgery and Nutrition Support
Program Director, Critical Care Residency
University of Michigan Hospitals and Health Centers
Ann Arbor, Michigan

Ronald W. Busuttil, MD, PhD
Distinguished Professor and Executive Chairman
UCLA Department of Surgery
David Geffen School of Medicine
University of California, Los Angeles
Los Angeles, California

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

Donna A. Caniano, MD
Professor of Surgery and Pediatrics
Department of Surgery
Ohio State University College of Medicine
Surgeon-in-Chief
Nationwide Children's Hospital
Columbus, Ohio

Michael G. Caty, MD
John E. Fisher Professor of Pediatric Surgery
Department of Pediatric Surgical Services
Women and Children's Hospital of Buffalo
Professor of Surgery and Pediatrics
Department of Surgery
State University of New York at Buffalo
Buffalo, New York

Christophe Chardot, MD, PhD
Professor
Universite Rene Descartes
Pediatric Surgery Unit
Hopital Necker Enfants Malades
Paris, France

Dai H. Chung, MD
Professor and Chairman
Janie Robinson and John Moore Lee Endowed Chair
Pediatric Surgery
Vanderbilt University Medical Center
Nashville, Tennessee

Robert E. Cilley, MD
Professor of Surgery and Pediatrics
Department of Surgery
Penn State College of Medicine
Hershey, Pennsylvania

Nadja C. Colon, MD
Surgical Research Fellow
Pediatric Surgery
Vanderbilt University Medical Center
Nashville, Tennesee

Paul M. Columbani, MD
Robert Garrett Professor of Surgery
Department of Surgery
The Johns Hopkins University School of Medicine
Pediatric Surgeon in Charge
The Johns Hopkins Hospital
Baltimore, Maryland

Arnold G. Coran, MD
Emeritus Professor of Surgery
Section of Pediatric Surgery
University of Michigan Medical School and C. S. Mott Children's Hospital
Ann Arbor, Michigan
Professor of Surgery
Division of Pediatric Surgery
New York University Medical School
New York, New York

Robin T. Cotton, MD, FACS, FRCS(C)
Director
Pediatric Otolaryngology–Head and Neck Surgery
Cincinnati Children's Hospital
Professor
Department of Otolaryngology
University of Cincinnati College of Medicine
Cincinnati, Ohio

Robert A. Cowles, MD
Assistant Professor
Department of Surgery
Columbia University College of Physicians and Surgeons
Assistant Attending Surgeon
Department of Surgery
Morgan Stanley Children's Hospital of New York–Presbyterian
New York, New York

Charles S. Cox, Jr., MD
The Children's Fund Distinguished Professor of Pediatric Surgery
Pediatric Surgery
University of Texas Medical School at Houston
Houston, Texas

Melvin S. Dassinger III, MD
Assistant Professor of Surgery
Department of Pediatric Surgery
University of Arkansas for Medical Sciences
Little Rock, Arkansas

Andrew M. Davidoff, MD
Chairman
Department of Surgery
St. Jude Children's Research Hospital
Memphis, Tennessee

Richard S. Davidson, MD
Division of Orthopedics
The Children's Hospital of Philadelphia
Philadelphia, Pennsylvania

Paolo De Coppi, MD, PhD
Clinical Senior Lecturer
Surgery Unit
University College of London Institute of Child Health
London, United Kingdom

Bryan J. Dicken, MD, MSc, FRCSC
Assistant Professor of Surgery
Pediatric Surgery
University of Alberta
Stollery Children's Hospital
Alberta, British Columbia, Canada

William Didelot, MD
Vice Chairman, Orthopedic Section
Pediatric Orthopedics
Peyton Manning Children's Hospital
Indianapolis, Indiana

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

Patrick A. Dillon, MD
Associate Professor of Surgery
Department of Surgery
Division of Pediatric Surgery
Washington University School of Medicine
St. Louis, Missouri

Peter W. Dillon, MD
Chair, Department of Surgery
John A. and Marian T. Waldhausen Professor of Surgery
The Pennsylvania State University College of Medicine
Hershey, Pennsylvania

Patricia K. Donahoe, MD
Marshall K. Bartlett Professor of Surgery
Harvard Medical School
Director, Pediatric Surgical Research Laboratories
Massachusetts General Hospital
Boston, Massachusettes

Gina P. Duchossois, MS
Injury Prevention Coordinator
Trauma Program
The Children's Hospital of Philadelphia
Philadelphia, Pennsylvania

James C. Y. Dunn, MD, PhD
Associate Professor
Surgery
University of California, Los Angeles School of Medicine
Los Angeles, California

Sanjeev Dutta, MD, MA
Associate Professor of Surgery and Pediatrics
Department of Surgery
Stanford University
Surgical Director
Multidisciplinary Initiative for Surgical Technology Research
Stanford University
SRI International
Stanford, California

Simon Eaton, BSc, PhD
Senior Lecturer
Surgery Unit
University College London Institute of Child Health
London, United Kingdom

Peter F. Ehrlich, MD, MSc
Associate Professor
Pediatric Surgery
University of Michigan C. S. Mott Children's Hospital
Ann Arbor, Michigan

Martin R. Eichelberger, MD
Professor of Surgery and Pediatrics
George Washington University
Children's National Medical Center
Washington, District of Columbia

Lisa M. Elden, MD, MS
Assistant Professor
Otorhinolaryngology
Head and Neck Surgery
University of Pennsylvania School of Medicine
Attending
Division of Otolaryngology
Department of Surgery
The Children's Hospital of Philadelphia
Philadelphia, Pennsylvania

Jonathan L. Eliason, MD
Assistant Professor of Vascular Surgery
Department of Surgery
University of Michigan
Ann Arbor, Michigan

Sherif Emil, MD, CM
Associate Professor and Director
Division of Pediatric General Surgery
Department of Surgery
Montreal Children's Hospital
McGill University Health Centre
Montreal, Quebec, Canada

Mauricio A. Escobar, Jr., MD
Pediatric Surgeon
Pediatric Surgical Services
Mary Bridge Children's Hospital and Health Center
Clinical Instructor
Department of Surgery
University of Washington
Tacoma, Washington

Richard A. Falcone, Jr., MD, MPH
Associate Professor of Surgery
Division of Pediatric and Thoracic Surgery
Department of Surgery
Cincinnati Children's Hospital Medical Center
University of Cincinnati College of Medicine
Cincinnati, Ohio

Mary E. Fallat, MD, FACS, FAAP
Hirikati S. Nagaraj Professor and Chief, Pediatric Surgery
Division Director, Pediatric Surgery
University of Louisville
Surgeon-in-Chief
Kosair Children's Hospital
Louisville, Kentucky

Diana L. Farmer, MD
Professor and Chair
Surgery School of Medicine
University of California Davis
Surgeon-in-Chief
University of California Davis Children's Hospital
Sacramento, California

Douglas G. Farmer, MD, FACS
Director, Intestinal Transplant Program
Co-Director, Intestinal Failure Center
University of California Los Angeles Medical Center
Los Angeles, California

Albert Faro, MD
Associate Professor of Pediatrics
Associate Medical Director
Pediatric Transplant Program
Pediatrics
Washington University
St. Louis Children's Hospital
St. Louis, Missouri

Michael J. Fisher, MD
Assistant Professor of Pediatrics
Department of Pediatrics
University of Pennsylvania School of Medicine
Attending Physician
Division of Oncology and Center for
Childhood Cancer Research
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania

Steven J. Fishman, MD
Associate Professor of Surgery
Children's Hospital Boston
Boston, Massachusettes

Tamara N. Fitzgerald, MD, PhD
Senior Resident, Department of Surgery
Yale University
New Haven, Connecticuit

Alan W. Flake, MD
Professor of Surgery
Director, Children's Center for Fetal Research
General, Thoracic, and Fetal Surgery
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania

Robert P. Foglia, MD
Professor, Division Chief, Pediatric Surgery
Hellen J. and Robert S. Strauss and Diana K. and Richard
C. Strauss Chair in Pediatric Surgery
Department of Surgery
University of Texas Southwestern
Surgeon-in-Chief
Children's Medical Center
Dallas, Texas

Henri R. Ford, MD, MHA
Vice President and Chief of Surgery
Pediatric Surgery
Children's Hospital Los Angeles
Professor and Vice Chair
Vice Dean of Medical Education
Department of Surgery
Keck School of Medicine
University of Southern California
Los Angeles, California

Andrew Franklin, MD
Clinical Fellow
Pediatric Anesthesiology
Monroe Carell Jr. Children's Hospital at Vanderbilt
Nashville, Tennesee

Jason S. Frischer, MD
Assistant Professor of Surgery
Pediatric General and Thoracic Surgery
University of Cincinnati School of Medicine
Cincinnati Children's Hospital Medical Center
Cincinnati, Ohio

Stephanie M. P. Fuller, MD
Assistant Professor
Surgery
University of Pennsylvania School of Medicine
Attending Surgeon
Division of Cardiothoracic Surgery
The Children's Hospital of Philadelphia
Philadelphia, Pennsylvania

Sanjiv K. Gandhi, MD
Associate Professor of Surgery
Surgery
British Columbia Children's Hospital
Vancouver, British Columbia, Canada

Victor F. Garcia, MD, FACS, FAAP
Founding Trauma Director, Professor of Surgery
Trauma Service, Pediatric Surgery
Cincinnati Children's Hospital
Courtesy Staff Surgery
University Hospital
Cincinnati, Ohio

John M. Gatti, MD
Associate Professor and Director of
Minimally Invasive Urology
Surgery and Urology
University of Missouri, Kansas City
Children's Mercy Hospital
Surgery and Urology
Associate Clinical Professor
Urology
University of Kansas School of Medicine
Kansas City, Missouri

Michael W. L. Gauderer, MD
Professor of Surgery and Pediatrics
Division of Pediatric Surgery
Children's Hospital
Greenville Hospital System University Medical Center
Greenville, South Carolina

James D. Geiger, MD
Professor of Surgery
Pediatric Surgery
University of Michigan
Ann Arbor, Michigan

Keith E. Georgeson, MD
Joseph M. Farley Professor of Surgery
Department of Surgery
Division of Pediatric Surgery
The University of Alabama School of Medicine
Birmingham, Alabama

Cynthia A. Gingalewski, MD
Assistant Professor of Surgery and Pediatrics
Department of Surgery
Children's National Medical Center
Washington, District of Columbia

Kenneth I. Glassberg, MD, FAAP, FACS
Director of Pediatric Urology
Professor of Urology
Columbia University Medical Center
New York, New York

Philip L. Glick, MD, MBA, FACS, FAAP, FRCS(Eng)
Vice Chairman
Department of Surgery
Professor of Surgery
Pediatrics and Obstetrics/Gynecology
State University of New York at Buffalo
Buffalo, New York

Kelly D. Gonzales, MD
Research Fellow
Division of Pediatric Surgery
University of California, San Francisco School of Medicine
San Francisco, California

Tracy C. Grikscheit, MD
Assistant Professor of Surgery
Department of Surgery
Division of Pediatric Surgery
University of Southern California, Los Angeles
Assistant Professor of Surgery
Department of Pediatric Surgery
Children's Hospital Los Angeles
Los Angeles, California

Jay L. Grosfeld, MD
Lafayette Page Professor of Pediatric Surgery and Chair, Emeritus
Section of Pediatric Surgery
Indiana University School of Medicine
Surgeon-in-Chief, Emeritus
Pediatric Surgery
Riley Children's Hospital
Indianapolis, Indiana

Travis W. Groth, MD
Pediatric Urology Fellow
Department of Pediatric Urology
Children's Hospital of Wisconsin
Milwaukee, Wisconsin

Angelika C. Gruessner, MS, PhD
Professor
Mel and Enid Zuckerman College of Public Health/ Epidemiology and Biostatistics
University of Arizona
Tucson, Arizona

Rainer W. G. Gruessner, MD
Professor, Chief of Surgery
Department of Surgery
University of Arizona College of Medicine
Surgery Clinical Service Chief
Surgery
University Medical Center
Tucson, Arizona

Ivan M. Gutierrez, MD
Pediatric Surgery Research Fellow
General Surgery
Children's Hospital Boston
Boston, Massachusettes

Philip C. Guzzetta, Jr., MD
Professor
Surgery and Pediatrics
George Washington University Medical Center
Pediatric Surgeon
Division of Pediatric Surgery
Children's National Medical Center
Washington, District of Columbia

Jason J. Hall, MD
Houston Plastic and Craniofacial Surgery
Houston, Texas

Thomas E. Hamilton, MD
Instructor in Surgery
Pediatric Surgery
Harvard Medical School
Adjunct Assistant Professor of Surgery and Pediatrics
Chief, Division of Pediatric Surgery
Boston University School of Medicine
Boston, Masachussettes

Carroll M. Harmon, MD, PhD
Professor of Surgery
Surgery
University of Alabama at Birmingham
Children's Hospital of Alabama
Birmingham, Alabama

Michael R. Harrison, MD
Professor of Surgery, Pediatrics, Obstetrics-Gynecology, and Reproductive Sciences, Emeritus
University of California, San Francisco
Attending
Surgery, Pediatrics, Obstetrics-Gynecology
University of California San Francisco Medical Center
San Francisco, California

Andrea Hayes-Jordan, MD, FACS, FAAP
Director
Pediatric Surgical Oncology
Surgical Oncology and Pediatrics
University of Texas MD Anderson Cancer Center
Houston, Texas

Stephen R. Hays, MD, MS, BS
Associate Professor
Anesthesiology and Pediatrics
Vanderbilt University Medical Center
Director
Pediatric Pain Services
Monroe Carell Jr. Children's Hospital at Vanderbilt
Nashville, Tennessee

John H. Healey, MD
Chief of Orthopaedic Surgery
Department of Surgery
Memorial Sloan-Kettering Cancer Center
Professor of Orthopaedic Surgery
Orthopaedic Surgery
Weill Cornell Medical College
Attending Orthopaedic Surgeon
Department of Orthopedic Surgery
Hospital for Special Surgery
New York, New York

W. Hardy Hendren III, MD
Chief, Emeritus
Robert E. Gross Distinguished Professor of Surgery
Children's Hospital Boston
Boston, Massachusetts

Bernhard J. Hering, MD
Professor of Surgery and Medicine
Surgery
University of Minnesota
Director, Islet Transplantation
University of Minnesota Medical Center
Scientific Director
Schulze Diabetes Institute
Minneapolis, Minnesota

David N. Herndon, MD
Professor, Jesse H. Jones Distinguished Chair in Burn Surgery
Surgery
University of Texas Medical Branch
Chief of Staff and Director of Research
Medical Staff
Shriner's Hospitals for Children
Galveston, Texas

Shinjiro Hirose, MD
Assistant Professor
Department of Surgery
University of California, San Francisco
San Francisco, California

Jennifer C. Hirsch, MD, MS
Assistant Professor of Surgery and Pediatrics
Pediatric Cardiac Surgery
University of Michigan Hospital
Ann Arbor, Michigan

Ronald B. Hirschl, MD
Head, Section of Pediatric Surgery
Surgeon-in-Chief
C. S. Mott Children's Hospital
Ann Arbor, Michigan

David M. Hoganson, MD
Department of Surgery
Children's Hospital Boston
Boston, Massachusetts

George W. Holcomb III, MD, MBA
Surgeon-in-Chief
Pediatric Surgery
Children's Mercy Hospital
Kansas City, Missouri

Michael E. Höllwarth, MD
University Professor
Head
Department of Pediatric Surgery
Medical University of Graz
Graz, Austria

B. David Horn, MD
Assistant Professor
Clinical Orthopaedic Surgery
University of Pennsylvania
Philadelphia, Pennsylvania

Charles B. Huddleston, MD
Professor of Surgery
Department of Cardiothoracic Surgery
Washington University School of Medicine
Professor of Surgery
Cardiothoracic Surgery
St. Louis Children's Hospital
St. Louis, Missouri

Raymond J. Hutchinson, MD, MS
Professor
Pediatrics
Associate Dean, Regulatory Affairs
University of Michigan
Ann Arbor, Michigan

John M. Hutson, DSc, MS, BS, FRACS, FAAP
Professor of Paediatric Surgery
Department of Pediatrics
University of Melbourne
Professor
Surgical Research
Murdoch Children's Research Institute
Melbourne, Austrailia

Grace Hyun, MD
Assistant Professor
Urology
Mount Sinai Medical School
Associate Director
Pediatric Urology
Urology
Mount Sinai Medical Center
New York, New York

Thomas H. Inge, MD, PhD
Associate Professor of Surgery
Department of Surgery
University of Cincinnati
Associate Professor of Surgery and Pediatrics
Division of Pediatric General and Thoracic Surgery
Cincinnati Children's Hospital Medical Center
Cincinnati, Ohio

Tom Jaksic, MD
W. Hardy Hendren Professor
Surgery
Harvard Medical School
Vice Chairman
Department of Pediatric General Surgery
Children's Hospital Boston
Boston, Massachusetts

Andrew Jea, MD
Assistant Professor
Department of Neurological Surgery
Baylor College of Medicine
Houston, Texas
Director of Neuro-Spine Program
Department of Surgery
Division of Pediatric Neurosurgery
Texas Children's Hospital
Houston, Texas

Martin Kaefer, MD
Associate Professor
Indiana University
Riley Hospital for Children
Indianapolis, Indiana

Kuang Horng Kang, MD
Research Fellow
Department of Surgery
Harvard Medical School
Research Fellow
Department of Surgery
Children's Hospital Boston
Boston, Massachusettes

Christopher J. Karsanac, MD
Assistant Professor
Pediatrics and Anesthesiology
Monroe Carell Jr. Children's Hospital at Vanderbilt
Nashville, Tennessee

Kosmas Kayes, MD
Pediatric Orthopedics
Peyton Manning Children's Hospital
Volunter Clinical Faculty
Orthopedics
Indiana University School of Medicine
Indianapolis, Indiana
Medical Director
Biomechanics Laboratory
Ball State University
Muncie, Indiana

Robert E. Kelly, Jr., MD
Pediatric Surgeon
Children's Surgical Specialty Group
Children's Hospital of the King's Daughter
Sentara Norfolk General Hospital
Norfolk, Virginia

Edward M. Kiely, FRCS(I), FRCS(Eng), FRCPCH
Consultant Pediatric Surgeon
Great Ormond Street Hospital for Children
London, United Kingdom

Michael D. Klein, MD
Arvin I. Philippart Chair and Professor of Surgery
Wayne State University School of Medicine
Children's Hospital of Michigan
Detroit, Michigan

Matthew J. Krasin, MD
Associate Member
Radiological Sciences
St. Jude Children's Research Hospital
Memphis, Tennessee

Thomas M. Krummel, MD
Emile Holman Professor and Chair
Department of Surgery
Stanford University School of Medicine
Susan B. Ford Surgeon-in-Chief
Lucile Packard Children's Hospital
Stanford, California

Ann M. Kulungowski, MD
Department of Surgery
Children's Hospital Boston
Boston, Massachusettes

Jean-Martin Laberge, MD
Professor of Surgery
McGill University
Attending Pediatric Surgeon
Montreal Children's Hospital of the McGill University Health Centre
Montreal, Quebec, Canada

Ira S. Landsman, MD
Chief
Division of Pediatric Anesthesiology
Vanderbilt Hospital
Nashville, Tennessee

Jacob C. Langer, MD
Professor of Surgery
Department of Surgery
University of Toronto
Chief and Robert M. Filler Chair
Division of General and Thoracic Surgery
Hospital for Sick Children
Toronto, Ontario, Canada

Michael P. La Quaglia, MD
Chief
Pediatric Surgery
Memorial Sloan-Kettering Cancer Center
Professor of Surgery
Weill Medical College of Cornell University
New York, New York

Marc R. Laufer, MD
Chief of Gynecology
Department of Surgery
Children's Hospital Boston
Center for Infertility and Reproductive Surgery
Brigham and Women's Hospital
Boston, Masachusettes

Hanmin Lee, MD
Associate Professor
Department of Surgery
University of California, San Francisco
Director
Fetal Treatment Center
University of California, San Francisco
San Francisco, California

Joseph L. Lelli, Jr., MD
Chief
Pediatric Surgery
Children's Hospital of Michigan
Detroit, Michigan

Marc A. Levitt, MD
Associate Professor
Cincinnati Children's Hospital Medical Center
Department of Surgery
Division of Pediatric Surgery
University of Cincinnati
Cincinnati, Ohio

James Y. Liau, MD
Craniofacial Fellow
Division of Plastic Surgery
Chapel Hill, North Carolina

Craig Lillehei, MD
Surgeon
Department of General Surgery
Children's Hospital Boston
Boston, Massachusettes

Harry Lindahl, MD, PhD
Associate Professor
Paediatric Surgery
Helsinki University Central Hospital Children's Hospital
Helinski, Finland

Gigi Y. Liu, MD, MSc
Research Assistant
Department of Surgery and Pediatrics
Stanford University
PGY-1
Department of Internal Medicine
Johns Hopkins University
Baltimore, Maryland

H. Peter Lorenz, MD
Professor of Plastic Surgery
Department of Surgery
Stanford University School of Medicine
Stanford, California
Service Chief
Plastic Surgery
Director
Craniofacial Anomalies Program
Plastic Surgery
Lucile Packard Children's Hospital
Palo Alto, California

Thomas G. Luerssen, MD, FACS, FAAP
Professor of Neurological Surgery
Department of Neurological Surgery
Baylor College of Medicine
Chief, Division of Pediatric Neurosurgery
Chief Quality Officer
Department of Surgery
Texas Children's Hospital
Houston, Texas

Jeffrey R. Lukish, MD
Associate Professor of Surgery
Surgery
Johns Hopkins University
Baltimore, Maryland

Dennis P. Lund, MD
Professor of Surgery
Surgery
University of Wisconsin School of Medicine and Public Health
Surgeon-in-Chief
American Family Children's Hospital
University of Wisconsin Hospital and Clinics
Chairman, Division of General Surgery
Surgery
University of Wisconsin School of Medicine and Public Health
Madison, Wisconsin

John C. Magee, MD
Associate Professor of Surgery
Department of Surgery
University of Michigan
Ann Arbor, Michigan

Eugene D. McGahren III, MD, BA
Professor of Pediatric Surgery and Pediatrics
Division of Pediatric Surgery
University of Virginia Health System
Charlottesville, Virginia

Eamon J. McLaughlin, MD
Medical Student
Department of Neurosurgery
University of Pennsylvania Medical Center
Medical Student
Department of Neurosurgery
The Children's Hospital of Philadelphia
Philadelphia, Pennsylvania

Leslie T. McQuiston, MD
Assistant Professor of Surgery
Urology and Pediatrics
Department of Surgery
Division of Pediatric Surgery
Dartmouth-Hitchcock Medical Center/Dartmouth Medical School
Lebanon, New Hampshire

Rebecka L. Meyers, MD
Chief of Pediatric Surgery
Division of Pediatric Surgery
University of Utah
Chief of Pediatric Surgery
Pediatric Surgery
Primary Children's Medical Center
Salt Lake City, Utah

Alastair J. W. Millar, DCH, MBChB, FRCS, FRACS, FCS(SA)
Charles F. M. Saint Professor of Pediatric Surgery
Institute of Child Health
University of Cape Town
Red Cross War Memorial Children's Hospital
Cape Town, South Africa

Eugene Minevich, MD, FAAP, FACS
Associate Professor
Pediatric Urology
Cincinnati Children's Hospital Medical Center
Cincinnati, Ohio

Edward P. Miranda, MD
Department of Plastic Surgery
California Pacific Medical Center
San Francisco, California

Michael E. Mitchell, MD
Professor and Chief
Pediatric Urology
Medical College of Wisconsin
Children's Hospital of Wisconsin
Milwaukee, Wisconsin

Kevin P. Mollen, MD
Assistant Professor of Surgery
Department of Surgery
University of Pittsburgh School of Medicine
Division of Pediatric General and Thoracic Surgery
Children's Hospital of Pittsburgh
Pittsburgh, Pennsylvania

R. Lawrence Moss, MD
Robert Pritzker Professor and Chief
Pediatric Surgery
Yale University School of Medicine
Surgeon-in-Chief
Yale New Haven Children's Hospital
New Haven, Connecticuit

Pierre Mouriquand, MD, FRCS(Eng), FEAPU
Professor, Directeur of Pediatric Urology
Pediatric Urology
Hôpital Mère-Enfants
Université Claude-Bernard
Lyon, France

Noriko Murase, MD
Associate Professor
Department of Surgery
University of Pittsburgh
Pittsburgh, Pennsylvania

J. Patrick Murphy, MD
Chief of Section of Urology
Department of Surgery
Children's Mercy Hospital
Professor of Surgery
Department of Surgery
University of Missouri at Kansas City
Kansas City, Missouri

Joseph T. Murphy, MD
Associate Professor
Division of Pediatric Surgery
University of Texas Southwestern Medical Center
Dallas, Texas

Michael L. Nance, MD
Director, Pediatric Trauma Program
The Children's Hospital of Philadelphia
Professor of Surgery
Surgery
University of Pennsylvania
Philadelphia, Pennsylvania

Saminathan S. Nathan, MBBS, Mmed, FRCS, FAMS
Associate Professor
Orthopedic Surgery
Yong Loo Lin School of Medicine
National University of Singapore
Head, Division of Musculoskeletal Oncology
Clinical Director
Department of Orthopaedic Surgery
Senior Consultant, Division of Hip and Knee Surgery
Principal Investigator
Musculoskeletal Oncology Research Laboratory
University Orthopaedics, Hand, and Reconstructive Microsurgery Cluster
National University Health System
Singapore

Kurt D. Newman, MD
Professor of Surgery and Pediatrics
Department of Surgery
The George Washington University Medical Center
President and Chief Executive Officer
Children's National Medical Center
Washington, District of Columbia

Alp Numanoglu, MD
Associate Professor
Department of Pediatric Surgery
Red Cross War Memorial Children's Hospital and University of Cape Town
Cape Town, South Africa

Benedict C. Nwomeh, MD, FACS, FAAP
Director of Surgical Education
Department of Pediatric Surgery
Nationwide Children's Hospital
Associate Professor of Surgery
Department of Surgery
The Ohio State University
Columbus, Ohio

Richard G. Ohye, MD
Associate Professor
Cardiac Surgery
University of Michigan
Section Head, Pediatric Cardiovascular Surgery
Cardiac Surgery
University of Michigan Health Systems
Ann Arbor, Michigan

Keith T. Oldham, MD
Professor and Chief
Division of Pediatric Surgery
Medical College of Wisconsin
Milwaukee, Wisconsin

James A. O'Neill, Jr., MD
J. C. Foshee Distinguished Professor and Chairman, Emeritus
Section of Surgical Sciences
Vanderbilt University School of Medicine
Nashville, Tennessee

Mikko P. Pakarinen, MD, PhD
Associate Professor in Pediatric Surgery
Pediatric Surgery
University of Helsinki
Consultant in Pediatric Surgery
Pediatric Surgery
Children's Hospital
University Central Hospital
Helsinki, Finland

Nicoleta Panait, MD
Chief Resident
Department of Pediatric Urology
Hôpital Mère-Enfants
Université Claude-Bernard
Lyon, France

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

Alberto Peña, MD
Director
Colorectal Center for Children
Pediatric Surgery
Cincinnati Children's Hosptial Medical Center
Cincinnati, Ohio

Rafael V. Pieretti, MD
Assistant Professor of Surgery
Harvard Medical School
Chief Section of Pediatric Urology
Massachusetts General Hospital
Boston, Massachusetts

Agostino Pierro, MD, FRCS(Engl), FRCS(Ed), FAAP
Nuffield Professor of Pediatric Surgery and
Head of Surgery Unit
University College London Institute of Child Health
Great Ormond Street Hospital for Children
London, United Kingdom

Hannah G. Piper, MD
Fellow Pediatric Surgery
Pediatric Surgery
University of Texas Southwestern
Fellow in Pediatric Surgery
Pediatric Surgery
Children's Medical Center
Dallas, Texas

William P. Potsic, MD, MMM
Professor of Otorhinolaryngology–Head and Neck Surgery
University of Pennsylvania Medical Center
Vice Chair for Clinical Affairs
Director of Ambulatory Surgical Services
Department of Surgery
The Children's Hospital of Philadelphia
Philadelphia, Pennsylvania

Howard I. Pryor II, MD
General Surgery Resident
Department of Surgery
George Washington University
Washington, District of Columbia
Surgical Research Fellow
Department of Surgery
Massachusetts General Hospital
Boston, Masachusettes

Pramod S. Puligandla, MD, MSc, FRCSC, FACS
Associate Professor of Surgery and Pediatrics
Departments of Surgery and Pediatrics
The McGill University Health Centre
Program Director
Division of Pediatric General Surgery
The Montreal Children's Hospital
Departments of Pediatric Surgery and Pediatric Critical Care
Medicine
The Montreal Children's Hospital
Montreal, Quebec, Canada

Prem Puri, MS, FRCS, FRCS(ED), FACS, FAAP(Hon.)
Newman Clinical Research Professor
University of Dublin
President
National Children's Research Centre
Our Lady's Children's Hospital
Crumlin, Dublin, Ireland
Consultant Pediatrician Surgeon/Pediatric Urologist
Beacon Hospital
Sandyford, Dublin, Ireland

Faisal G. Qureshi, MD
Assistant Professor Surgery and Pediatrics
Department of Pediatric Surgery
Children's National Medical Center
Washington, District of Columbia

Frederick J. Rescorla, MD
Professor of Surgery
Department of Surgery
Indiana University School of Medicine
Surgeon-in-Chief
Riley Hospital for Children
Clarian Health Partners
Indianapolis, Indiana

Yann Révillon, MD
Professor
Université René Descartes
Pediatric Surgery Unit
Hôpital Necker Enfants Malades
Paris, France

Jorge Reyes, MD
Director of Pediatric Solid Organ Transplant Services
Surgery
Seattle Children's Hospital
Chief
Division of Transplant Surgery
Surgery
University of Washington
Seattle, Washington
Medical Director
LifeCenter Northwest Organ Donation Network
Bellevue, Washington

Marleta Reynolds, MD
Lydia J. Fredrickson Professor of Pediatric Surgery
Department of Surgery
Northwestern University's Feinberg School of Medicine
Surgeon-in-Chief and Head
Department of Surgery
Children's Memorial Hospital
Chicago, Illnois
Department of Surgery
Northwestern Lake Forest Hospital
Lake Forest, Illinois
Attending
Department of Surgery
Northwestern Community Hospital
Arlington Heights, Illinois

Audrey C. Rhee, MD
Indiana University
Department of Urology
Riley Hospital for Children
Indianapolis, Indiana

Barrie S. Rich, MD
Clinical Research Fellow
Memorial Sloan-Kettering Cancer Center
New York, New York

Richard R. Ricketts, MD
Professor of Surgery
Chief
Department of Surgery
Division of Pediatric Surgery
Emory University
Atlanta, Georgia

Richard C. Rink, MD, FAAP, FACS
Professor and Chief
Pediatric Urology
Riley Hospital for Children
Robert A. Garrett Professor of Pediatric Urologic Research
Pediatric Urology
Indiana University School of Medicine
Indianapolis, Indiana

Risto J. Rintala, MD, PhD
Professor of Pediatric Surgery
Department of Pediatric Surgery
Hospital for Children and Adolescents
University of Helsinki
Helsinki, Finland

Albert P. Rocchini, MD
Professor of Pediatrics
Pediatrics
University of Michigan
Ann Arbor, Michigan

David A. Rodeberg, MD
Co-Director and Surgeon-in-Chief of the
Maynard Children's Hospital
The Verneda and Clifford Kiehn Professor of Pediatric Surgery
Chief, Division of Pediatric Surgery
Department of Surgery
Brody School of Medicine
East Carolina University
Greenville, North Carolina

A. Michael Sadove, MD, FACS, FAAP
James Harbaugh Endowed Professor of Surgery, Retired
Indiana University School of Medicine
Professor of Oral and Maxillofacial Surgery
Indiana University School of Dentistry
Indiana University North Hospital
President of the Medical Staff
Director of Cleft Program
Peyton Manning Children's Hospital
St. Vincent Medical Center
Indianapolis, Indiana

Bob H. Saggi, MD, FACS
Associate Professor of Surgery
Clinical Professor of Pediatrics
Tulane University School of Medicine
Associate Program Director
Liver Transplantation and Hepatobiliary Surgery
Tulane University Medical Center
Abdominal Transplant Institute
New Orleans, Louisiana

L. R. Scherer III, MD, BS
Professor
Surgery
Director
Trauma Services
Riley Hospital for Children
Indianapolis, Indiana

Daniel B. Schmid, MD, BA
Resident Physician
Plastic and Reconstructive Surgery
University of Wisconsin
Madison, Wisconsin

Stefan Scholz, MD, PhD
Chief Resident in Pediatric Surgery
Department of Surgery
Division of Pediatric Surgery
Johns Hopkins University
Baltimore, Maryland

Marshall Z. Schwartz, MD
Professor of Surgery and Pediatrics
Drexel University College of Medicine
Surgeon-in-Chief
Chief, Pediatric Surgery
St. Christopher's Hospital for Children
Philadelphia, Pennsylvania

Robert C. Shamberger, MD
Chief of Surgery
Children's Hospital Boston
Robert E. Gross Professor of Surgery
Harvard Medical School
Boston, Massachusetts

Nina L. Shapiro, MD
Associate Professor
Surgery/Division of Head and Neck Surgery
University of California, Los Angeles School of Medicine
Los Angeles, California

Curtis A. Sheldon, MD
Director
Urogenital Center
Professor
Division of Pediatric Surgery
Cincinnati Children's Hospital Medical Center
Cincinnati, Ohio

Stephen J. Shochat, MD
Professor
Department of Surgery
St. Jude Children's Research Hospital
Memphis, Tennessee

Douglas Sidell, MD
Resident Physician
Department of Surgery
Division of Head and Neck Surgery
University of California, Los Angeles
Los Angeles, California

Michael A. Skinner, MD
Professor
Department of Pediatric Surgery and General Surgery
The University of Texas Southwestern Medical School
Dallas, Texas

Jodi L. Smith, MD, PhD
John E. Kalsbeck Professor and Director of Pediatric Neurosurgery
Neurological Surgery
Riley Hospital for Children
Indiana University School of Medicine
Indianapolis, Indiana

Samuel D. Smith, MD
Chief of Pediatric Surgery
Division of Pediatric Surgery
Arkansas Children's Hospital
Boyd Family Professor of Pediatric Surgery
Surgery
University of Arkansas for Medical Sciences
Little Rock, Arkansas

Charles L. Snyder, MD
Professor of Surgery
Department of Surgery
University of Missouri at Kansas City
Kansas City, Missouri

Allison L. Speer, MD
General Surgery Resident
Department of Surgery
University of Southern California, Los Angeles
Research Fellow
Department of Pediatric Surgery
Children's Hospital, Los Angeles
Los Angeles, California

Lewis Spitz, MD(Hon.), PhD, FRCS, FAAP(Hon.), FRCPCH(Hon.), FCS(SA)(Hon.)
Emeritus Nuffield Professor of Paediatric Surgery
Institute of Child Health
University College, London
Great Ormond Street Hospital for Children
London, United Kingdom

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

James C. Stanley, MD
Handleman Professor of Surgery
Department of Surgery
University of Michigan, Ann Arbor
Director, Cardiovascular Center
University of Michigan
Ann Arbor, Michigan

Thomas E. Starzl, MD, PhD
Professor of Surgery
University of Pittsburgh
Montefiore Hospital
Professor of Surgery
Director Emeritus Thomas E. Starzl Transplantation Institute
VA Distinguished Service Professor
Pittsburgh, Pennsylvania

Wolfgang Stehr, MD
Attending Surgeon
Pediatric Surgical Associates of the East Bay, Children's Hospital and Research Institute
Oakland, California

Charles J. H. Stolar, MD
Professor of Surgery and Pediatrics
Surgery
Columbia University
College of Physicians and Surgeons
New York, New York

Phillip B. Storm, MD
Assistant Professor of Neurosurgery
Department of Neurosurgery
The Children's Hospital of Philadelphia
Philadelphia, Pennsylvania

Steven Stylianos, MD
Professor of Surgery and Pediatrics
Hofstra University North Shore–LIJ School of Medicine
Hempstead, New York
Chief, Division of Pediatric Surgery
Associate Surgeon-in-Chief
Cohen Children's Medical Center of New York
New Hyde Park, New York

Ramnath Subramaniam, MBBS, MS(Gen Surg), MCh (Paed), FRCSI, FRCS(Paed), FEAPU, PG Cl Edn
Pediatric Surgery and Urology
Leeds Teaching Hospitals NHS Trust
Leeds, United Kingdom

Riccardo Superina, MD
Professor
Department of Surgery
Feinberg School of Medicine
Northwestern University
Director, Transplant Surgery
Department of Surgery
The Children's Memorial Hospital
Chicago, Illinois

David E. R. Sutherland, MD, PhD
Professor of Surgery
Schulze Diabetes Institute and Department of Surgery
University of Minnesota
Minneapolis, Minnesota

Leslie N. Sutton, MD
Professor
University of Pennsylvania School of Medicine
Chief, Division of Neurosurgery
Director, Neurosurgery Fellowship Program
The Children's Hospital of Philadelphia
Philadelphia, Pennsylvania

Roman Sydorak, MD
Pediatric Surgeon
Kaiser Los Angeles Medical Center
Division of Pediatric Surgery
Los Angeles, California

Karl G. Sylvester, MD
Associate Professor
Department of Surgery and Pediatrics
Stanford University School of Medicine
Stanford, California
Lucile Packard Children's Hospital
Palo Alto, California

Daniel H. Teitelbaum, MD
Professor of Surgery
Surgery
University of Michigan
Ann Arbor, Michigan

Joseph J. Tepas III, MD, FACS, FAAP
Professor of Surgery and Pediatrics
Surgery
University of Florida College of Medicine
Jacksonville, Florida

John C. Thomas, MD, FAAP
Assistant Professor of Urologic Surgery
Division of Pediatric Urology
Monroe Carell Jr. Children's Hospital at Vanderbilt
Nashville, Tennessee

Dana Mara Thompson, MD, MS
Chair, Division of Pediatric Otolaryngology
Department of Otorhinolaryngology
Head and Neck Surgery
Mayo Clinic
Associate Professor of Otolaryngology
Mayo Clinic College of Medicine
Rochester, Minnesota

Juan A. Tovar, MD, PhD, FAAP(Hon.), FEBPS
Professor and Chief Surgeon
Pediatric Surgery
Hospital Universitario La Paz
Madrid, Spain

Jeffrey S. Upperman, MD
Director
Trauma Program
Associate Professor of Surgery
Pediatric Surgery
Children's Hospital, Los Angeles
Los Angeles, California

Joseph P. Vacanti, MD
Surgeon-in-Chief
Department of Pediatric Surgery
Director
Pediatric Transplantation Center
Massachusetts General Hospital
Boston, Massachusetts

John A. van Aalst, MD, MA
Director of Pediatric and Craniofacial Plastic Surgery
Department of Surgery
Division of Plastic Surgery
University of North Carolina
Chapel Hill, North Carolina

Dennis W. Vane, MD, MBA
J. Eugene Lewis Jr., MD, Professor and Chair of Pediatric Surgery
Department of Surgery
St. Louis University
Surgeon-in-Chief
Cardinal Glennon Children's Medical Center
St. Louis, Missouri

Daniel Von Allmen, MD
Professor of Surgery
Department of Surgery
University of Cincinnati College of Medicine
Director
Division of Pediatric Surgery
Department of Surgery
Cincinnati Children's Hospital
Cincinnati, Ohio

Kelly Walkovich, MD
Clinical Lecturer
Pediatrics and Communicable Diseases
University of Michigan
Clinical Lecturer
Pediatrics and Communicable Diseases
University of Michigan Medical School
Ann Arbor, Michigan

Danielle S. Walsh, MD, FACS, FAAP
Associate Professor
Surgery
East Carolina University
Surgery
Pitt County Memorial Hospital
Maynard Children's Hospital
Greenville, North Carolina

Brad W. Warner, MD
Jessie L. Ternberg, MD, PhD, Distinguished Professor of Pediatric Surgery
Department of Surgery
Washington University School of Medicine
Surgeon-in-Chief
Director
Division of Pediatric General Surgery
St. Louis Children's Hospital
St. Louis, Missouri

Thomas R. Weber, MD
Director
Pediatric General Surgery
Advocate Hope Children's Hospital
Professor
Pediatric Surgery
University of Illinois
Chicago, Illinois

Christopher B. Weldon, MD, PhD
Instructor in Surgery
Department of Surgery
Harvard Medical School
Assistant in Surgery
Department of Surgery
Children's Hospital Boston
Boston, Massachusetts

David E. Wesson, MD
Professor
Department of Surgery
Baylor College of Medicine
Houston, Texas

Ralph F. Wetmore, MD
E. Mortimer Newlin Professor of Pediatric Otolaryngology
The Children's Hospital of Philadelphia
University of Pennsylvania School of Medicine
Philadelphia, Pennsylvania
Chief
Division of Pediatric Otolaryngology
The Children's Hospital of Philadelphia
Philadelphia, Pennsylvania

J. Paul Willging, MD
Professor
Otolaryngology–Head and Neck Surgery
University of Cincinnati College of Medicine
Cincinnati Children's Hospital Medical Center
Cincinnati, Ohio

Jay M. Wilson, MD, MS
Associate Professor of Surgery
Department of Surgery
Harvard Medical School
Senior Associate in Surgery
Department of Surgery
Children's Hospital Boston
Boston, Masachusettes

Lynn L. Woo, MD
Assistant Professor
Pediatric Urology
Case Western Reserve University College of Medicine
Pediatric Urology
Rainbow Babies and Children's Hospital
University Hospitals of Cleveland
Cleveland, Ohio

Russell K. Woo, MD
Assistant Clinical Professor of Surgery
Department of Surgery
University of Hawaii
Honolulu, Hawaii

Elizabeth B. Yerkes, MD
Associate Professor
Department of Urology
Northwestern University Feinberg School of Medicine
Attending Pediatric Urologist
Division of Pediatric Urology
Children's Memorial Hospital
Chicago, Illinois

Moritz M. Ziegler, MD, MA(Hon.), MA(Hon.), BS
Surgeon-in-Chief, Retired
Ponzio Family Chair, Retired
Department of Surgery
The Children's Hospital, Denver, Colorado
Professor of Surgery, Retired
Department of Surgery
University of Colorado
Denver School of Medicine
Denver, Colorado

Arthur Zimmermann, MD
Professor of Pathology, Emeritus
Director
Institute of Pathology
University of Bern
Bern, Switzerland

Preface

In June 1959, a group of five distinguished pediatric surgeons from the United States and Canada formed an editorial board to investigate the possibility of writing an authoritative, comprehensive textbook of pediatric surgery. The five individuals assembled were Kenneth Welch, who served as chairman of the board from Boston Children's Hospital (the original name); Mark Ravitch from The Johns Hopkins Hospital; Clifford Benson from Detroit Children's Hospital (the original name); William Snyder from Los Angeles Children's Hospital; and William Mustard from The Hospital for Sick Children in Toronto, Canada. From 1953 to 1962, the most comprehensive textbook of pediatric surgery was *The Surgery of Infancy and Childhood* by Robert E. Gross. At that time, Dr. Gross had no plans to write a second edition of his book. He was the sole author of the first edition of his book and did not wish to carry out such a monumental task with a second edition. The five editors thought that an updated textbook of pediatric surgery was needed. The first edition was published in 1962 and quickly became recognized as the most definitive and comprehensive textbook in the field. Between 1962 and 2006, six editions of the book were published. During this period, this textbook has been considered the bible of pediatric surgery. The editors and authors have changed during the 44 years that elapsed from the first to the sixth editions. In most cases, the editorial board changed gradually with the deletion and addition of two to three pediatric surgeons with each edition. The editors of the fifth edition also continued as the editors of the sixth edition. In the current seventh edition, the editorial board has been replaced except for Arnold Coran, who has functioned as the Chief Editor of this edition, and Anthony Caldamone, who continues to be the editor for the urology section. A new generation of pediatric surgical leaders has emerged since the last edition, and the editorial board reflects that change. Robert Shamberger from Children's Hospital Boston, Scott Adzick from The Children's Hospital of Philadelphia, Thomas Krummel from the Lucile Packard Children's Hospital and Stanford University Medical Center, and Jean-Martin Laberge from the Montreal Children's Hospital of the McGill University Health Centre represent the new members of the editorial board.

The seventh edition continues its international representation, with authors from several countries contributing chapters. Most of the previous chapters have been retained, but, in several cases, new authors have been assigned to these chapters. Of special interest is the addition of a new chapter (Chapter 16) on patient- and family-centered pediatric surgical care, a relatively new concept in the management of the pediatric surgical patient. Two chapters from the sixth edition, "Bone and Joint Infections" and "Congenital Defects of Skin, Connective Tissues, Muscles, Tendons, and Joints," have been deleted because currently, most pediatric surgeons do not deal with these problems. A few of the urology chapters have been merged, but all the material from the previous edition is included in these chapters. The chapter "Congenital Heart Disease and Anomalies of the Great Vessels" (Chapter 127) was kept comprehensive because so many of these patients have co-existent pediatric surgical problems or have surgical problems after cardiac surgery. Overall, there are 131 chapters in this edition, all of which are written by experts in the field and represent a comprehensive treatise of the subject with an exhaustive bibliography. In addition, each chapter provides a complete discussion of both open and closed techniques, when appropriate, for the management of the surgical problem.

One of the remarkable things about this edition is that not a single sheet of paper was used by the authors or editors in the creation of the book. Everything from the writing of the chapter to its editing was done electronically. This entire process was overseen by Lisa Barnes, the developmental editor at Elsevier. All the editors wish to thank her for her patience, availability, and efficiency in completing this textbook. Finally, we want to thank all the authors for their outstanding chapters, which will provide definitive and comprehensive information on the various pediatric surgical problems to pediatric surgeons throughout the world and thus improve the surgical care of infants and children worldwide.

The Editors

CHAPTER 1

History of Pediatric Surgery: A Brief Overview

Jay L. Grosfeld and James A. O'Neill Jr.

The history of pediatric surgery is rich, but only the major contributions and accounts of the leaders in the field can be summarized here.

Early Years

The development of pediatric surgery has been tightly bound to that of surgery in adults, and in general, surgical information was based on simple observations of obvious deformities, such as cleft lip and palate, skeletal deformities, and imperforate anus. The only basic science of the 2nd through 16th centuries, until the 19th, was anatomy, mostly developed by surgeons; so, technical care was based on this, regardless of the patient's age. The fate of affected infants with a defect was frequently related to the cultural and societal attitudes of the time, and most did not survive long. A better understanding of the human body was influenced by Galen's study of muscles, nerves, and blood vessels in the 2nd century.[1] Albucacis described circumcision, use of urethral sounds, and cleft lip in Cordoba in the 9th century.[2] Little progress was made during the Middle Ages. In the 15th and 16th centuries, Da Vinci provided anatomic drawings; Vesalius touched on physiology; and Ambrose Paré, better known for his expertise in war injuries, wrote about club foot and described an omphalocele and conjoined twins.[3] The 17th and 18th centuries were the era of the barber surgeon. Johannes Fatio, a surgeon in Basel, was the first to systematically study and treat surgical conditions in children, and he attempted separation of conjoined twins in 1689.[4] Other congenital malformations were identified as a result of autopsy studies, including descriptions of esophageal atresia in one of thoracopagus conjoined twins by Durston in 1670,[5] intestinal atresia by Goeller in 1674,[6] an instance of probable megacolon by Ruysch in 1691,[7] and a more precise description of esophageal atresia by Gibson in 1697,[8] but there were no attempts at operative correction. Surgery for children was usually limited to orthopedic procedures, management of wounds, ritual circumcision, and drainage of superficial abscesses. In 1793, Calder[9] was the first to describe duodenal atresia. In France, Duret[10] performed the initial colostomy for a baby with imperforate anus in 1793, Amussat[11] performed the first formal perineal anoplasty in 1834, and in the United States, Jacobi[12] performed the first colostomy for probable megacolon in 1869. Up to this point, no surgeon devoted his practice exclusively to children. Despite this fact, a movement began to develop hospitals for children, led mainly by women in various communities, who felt that adult hospitals were inappropriate environments for children.

In Europe, the major landmark in the development of children's hospitals was the establishment of the Hôpital des Enfants Malades in Paris in 1802, which provided treatment for children with both medical and surgical disorders.[13] Children younger than 7 years of age were not admitted to other hospitals in Paris. Subsequently, similar children's hospitals were established in major European cities, including Princess Lovisa Hospital in Stockholm in 1854, and other facilities followed in St. Petersburg, Budapest, East London, and Great Ormond Street, London.[14] Children's hospitals in the United States opened in Philadelphia (1855), Boston (1869), Washington, DC (1870), Chicago (1882), and Columbus, Ohio (1892).[15] The Hospital for Sick Children in Toronto was established in 1885. Some of these facilities started out as foundling homes and then mainly cared for orthopedic problems and medical illnesses. Few had full-time staff, because it was difficult to earn a living caring for children exclusively.

Major advances in the 19th century that would eventually influence surgical care were William T.G. Morton's introduction of anesthesia in 1864, antisepsis using carbolic acid championed by Joseph Lister and Ignaz Semelweiss in 1865, and Wilhelm Roentgen's discovery of the x-ray in 1895. Harald Hirschsprung of Copenhagen wrote a classical treatise on two infants with congenital megacolon in 1886,[16] and Max Wilms, then in Leipzig, described eight children with renal tumors in 1899.[17] Fockens accomplished the first successful anastomosis for intestinal atresia in 1911[18]; Pierre Fredet (1907)[19] and Conrad Ramstedt (1912)[20] documented effective operative procedures (pyloromyotomy) for hypertrophic pyloric stenosis; and N.P. Ernst did the first successful repair of duodenal atresia in 1914, which was published 2 years later.[21]

20th Century: The Formative Years

UNITED STATES

There was little further progress in the early 20th century because of World War I and the Great Depression. It was during this time that a few individuals emerged who would devote their total attention to the surgical care of children. William E. Ladd of Boston, Herbert Coe of Seattle, and Oswald S. Wyatt of Minneapolis, the pioneers, set the stage for the future of pediatric surgery in the United States.[14,15,22]

Ladd, a Harvard medical graduate in 1906, trained in general surgery and gynecology and was on the visiting staff at the Boston Children's Hospital. After World War I, he spent more time there and subsequently devoted his career to the surgical care of infants and children and became surgeon-in-chief in 1927. His staff included Thomas Lanman, who attempted repair of esophageal atresia in more than 30 patients unsuccessfully, but the report of his experience set the stage for further success. Ladd recruited Robert E. Gross, first as a resident and then as a colleague. Ladd developed techniques for management of intussusception, pyloric stenosis, and bowel atresia; did the first successful repair of a correctable form of biliary atresia in 1928; and described the Ladd procedure for intestinal malrotation in 1936 (Fig. 1-1, *A* and *B*).[23–26] While Ladd was out of Boston, and against his wishes, Gross, then 33 years old and still a resident, performed the first ligation of a patent ductus arteriosus in 1938. One can imagine how this influenced their relationship. Nonetheless, in 1941, Ladd and Gross published their seminal textbook, *Abdominal Surgery of Infants and Children.*[27] 1941 was of importance not only because of the entry of the United States into WW II, but that was the year that Cameron Haight,[28] a thoracic surgeon in Ann Arbor, Michigan, and Rollin Daniel, in Nashville, Tennessee, independently performed the first successful primary repairs of esophageal atresia.

In addition to his landmark ductus procedure, Gross' surgical innovations, involving the great vessels around the heart, coarctation of the aorta, management of vascular ring deformities, and early use of allografts for aortic replacement, were major contributions to the development of vascular surgery (Fig. 1-2).[14] The training program in Boston grew and recruited future standouts in the field, such as Alexander Bill, Orvar Swenson, Tague Chisholm, and H. William Clatworthy. Ladd retired in 1945 and was succeeded by Gross as surgeon-in-chief. Gross was a very skillful pediatric surgeon and cardiovascular surgical pioneer who continued to attract bright young trainees to his department. In 1946, C. Everett Koop and Willis Potts spent a few months observing at the Boston Children's Hospital and then returned to the Children's Hospital of Philadelphia and Children's Memorial Hospital in Chicago, respectively. Luther Longino, Judson Randolph, Morton Wooley, Daniel Hays, Thomas Holder, W. Hardy Hendren, Lester Martin, Theodore Jewett, Ide Smith, Samuel Schuster, Arnold Colodny, Robert Filler, Arvin Phillipart, and Arnold Coran were just a few of the outstanding individuals attracted to the Boston program. Many became leaders in the field, developed their own training programs and, like disciples, spread the new gospel of pediatric surgery across the country. After Gross retired, Judah Folkman, a brilliant surgeon-scientist, became the third surgeon-in-chief in Boston in 1968. W. Hardy Hendren, Moritz Ziegler, and, currently, Robert Shamberger followed in the leadership role at the Children's Hospital, Boston.[15,25]

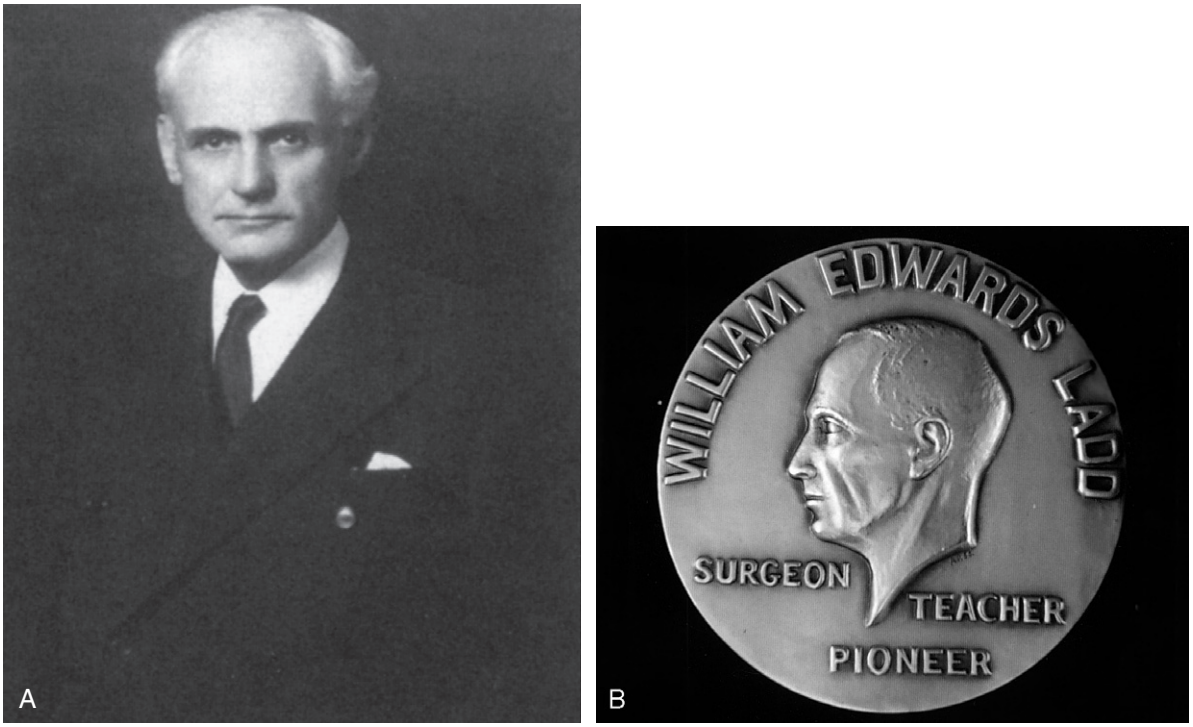


FIGURE 1-1 **A,** William E. Ladd. **B,** To honor Dr. Ladd's pioneering achievements, the Ladd Medal was established by the Surgical Section of the American Academy of Pediatrics to award individuals for outstanding achievement in pediatric surgery.

FIGURE 1-2 Robert E. Gross.

FIGURE 1-3 **A,** Herbert Coe, Seattle, Washington. **B,** Photograph of the first meeting of the Section on Surgery, American Academy of Pediatrics, November 12, 1948. Seated, from *left to right,* are Drs. William E. Ladd, Herbert Coe, Frank Ingraham, Oswald Wyatt, Thomas Lanman, and Clifford Sweet. Standing, from *left to right,* are Drs. Henry Swan, J. Robert Bowman, Willis Potts, Jesus Lozoya-Solis (of Mexico), C. Everett Koop, and Professor Fontana.

Herbert Coe was raised in Seattle, Washington, and attended medical school at the University of Michigan. After training in general surgery, he returned to Seattle in 1908 and was on staff at the Children's Orthopedic Hospital. After WWI, he spent time at the Boston Children's Hospital as an observer, gaining experience in pediatric surgical care. When he returned to Seattle in 1919, he was the first to exclusively limit his practice to pediatric surgery. He initiated the first children's outpatient surgical program in the country. He was a strong advocate for children and, in 1948, helped to persuade the leadership of the American Academy of Pediatrics (AAP) to form its surgery section, which he saw as a forum for pediatric surgeons to gather, share knowledge, and gain recognition for their new specialty (Fig. 1-3). Alexander Bill joined Coe in practice following his training in Boston and subsequently became surgeon-in-chief at the Children's Orthopedic Hospital.[14,15]

Oswald Wyatt, a Canadian by birth, attended both undergraduate school and medical school at the University of Minnesota. He trained in general surgery in Minneapolis. After serving in the military in WWI, Wyatt returned to Minneapolis and entered surgical practice. In 1927, he spent time with Edwin Miller at the Children's Memorial Hospital in Chicago. When he returned to Minneapolis, he then limited his surgical practice to children. When Tague Chishom completed his training with Ladd and Gross in 1946, he joined Wyatt's practice. Together they developed one of the largest and most successful pediatric surgery community practice groups in the country.[14,15]

In 1948, C. Everett Koop became the first surgeon-in-chief at the Children's Hospital in Philadelphia and served until 1981. He was followed by James A. O'Neill and subsequently Scott Adzick. Prominent trainees from this program include William Kiesewetter, Louise Schnaufer, Dale Johnson, John Campbell, Hugh Lynn, Judah Folkman, Howard Filston, John Templeton, Moritz Ziegler, Don Nakayama, Ron Hirschl, and others. Dr. Koop was the second president of the American Pediatric Surgical Association (APSA) and also served as Surgeon General of the United States from 1981 to 1989 (Fig. 1-4).

Also in 1948, Orvar Swenson performed the first successful rectosigmoidectomy operation for Hirschsprung disease at Boston Children's Hospital (Fig. 1-5).[29] In 1950, he became surgeon-in-chief of the Boston Floating Hospital and subsequently succeeded Potts as surgeon-in-chief at the Children's Memorial Hospital in Chicago.

H. William Clatworthy, the last resident trained by Ladd and Gross' first resident, continued his distinguished career as surgeon-in-chief at the Columbus Children's Hospital, (now Nationwide Children's Hospital) at Ohio State University in 1950 (Fig. 1-6). Clatworthy was a gifted teacher and developed a high-quality training program that produced numerous graduates who became leaders in the field and professors of pediatric surgery at major universities, including

FIGURE 1-4 C. Everett Koop.

FIGURE 1-6 H. William Clatworthy, Jr.

FIGURE 1-5 Orvar Swenson.

Peter Kottmeier (Brooklyn), Jacques Ducharme (Montreal,) Lloyd Schulz (Omaha), James Allen (Buffalo), Beimann Othersen (Charleston), Dick Ellis (Ft. Worth), Alfred de Lorimier (San Francisco), Eric Fonkalsrud (Los Angeles), Marc Rowe (Miami and Pittsburgh), James A. O'Neill (New Orleans, Nashville, and Philadelphia), Jay Grosfeld (Indianapolis), Neil Feins (Boston), Arnold Leonard (Minneapolis), and Medad Schiller (Jerusalem).[25] E. Thomas Boles succeeded Dr. Clatworthy as surgeon-in-chief in 1970.

EDUCATION, ORGANIZATIONAL CHANGES, AND RELATED ACTIVITIES

Following World War II, a glut of military physicians returned to civilian life and sought specialty training. A spirit of academic renewal and adventure then pervaded an environment influenced by the advent of antibiotics, designation of anesthesia as a specialty, and the start of structured residency training programs in general surgery across the country. By 1950, one could acquire training in children's surgery as a preceptor or as a 1- or 2-year fellow at Boston Children's Hospital (Gross), Children's Memorial Hospital in Chicago (Potts), Children's Hospital of Philadelphia (Koop), Boston Floating Hospital (Swenson), Babies' Hospital in New York (Thomas Santulli), or the Children's Hospital of Los Angeles (William Snyder). There were two established Canadian programs in Toronto and Montreal. The training program at the Columbus Children's Hospital (Clatworthy) started in 1952. Other programs followed in Detroit (C. Benson), Cincinnati (L. Martin), Pittsburgh (Kiesewetter), and Washington, DC (Randolph). The output of training programs was sporadic, and some graduates had varied experience in cardiac surgery and urology, but all had broad experience in general and thoracic pediatric surgery. Gross published his renowned textbook, *The Surgery of Infancy and Childhood,* in 1953.[30] This extraordinary text, the "Bible" of the fledgling field, described in detail the experience at Boston Children's Hospital in general pediatric surgery, cardiothoracic

surgery, and urology and became the major reference source for all involved in the care of children. The successor to this book, *Pediatric Surgery,* originally edited by Clifford Benson, William Mustard, Mark Ravitch, William Snyder, and Kenneth Welch was first published in two volumes in 1962 and has now gone through seven editions. It continues to be international and encyclopedic in scope, covering virtually every aspect of children's surgery. Over time, Judson Randolph, E. Aberdeen, James O'Neill, Marc Rowe, Eric Fonkalsrud, Jay Grosfeld, and Arnold Coran were added as editors through the sixth edition. As the field has grown, several other excellent texts have been published, adding to the rich literature in pediatric surgery and its subspecialties.

The 1950s saw an increasing number of children's surgeons graduating from a variety of training programs in the United States and Canada. Many entered community practice. A number of children's hospitals sought trained pediatric surgeons to direct their surgical departments, and medical schools began to recognize the importance of adding trained pediatric surgeons to their faculties. In 1965, Clatworthy requested that the surgical section of the AAP form an education committee whose mandate was to evaluate existing training programs and make recommendations for the essential requirements for educating pediatric surgeons. Originally, 11 programs in the United States and 2 in Canada met the standards set forth by the Clatworthy committee. In short order, additional training programs, which had been carefully evaluated by the committee, implemented a standard curriculum for pediatric surgical education.[14,15,31,32]

In the 1960s, a number of important events occurred that influenced the recognition of pediatric surgery as a bona fide specialty in North America.[33] Lawrence Pickett, then secretary of the AAP Surgical Section, and Stephen Gans were strong proponents of the concept that the specialty needed its own journal. Gans was instrumental in starting the *Journal of Pediatric Surgery* in 1966, with Koop serving as the first editor-in-chief.[34] Eleven years later, Gans succeeded Koop as editor-in-chief, a position he held until his death in 1994. Jay Grosfeld then assumed the role and continues to serve as editor-in-chief of the *Journal of Pediatric Surgery* and the *Seminars of Pediatric Surgery,* which was started in 1992.

Lucian Leape, Thomas Boles, and Robert Izant promoted the concept of a new independent surgical society, in addition to the surgical section of the AAP. The idea was quickly embraced by the pediatric surgical community, and the American Pediatric Surgical Association (APSA) was launched in 1970, with Gross serving as its first president.[35,36]

In the 1950s and 1960s, three requests to the American Board of Surgery (ABS) to establish a separate board in Pediatric Surgery were unsuccessful. However, with the backing of a new independent surgical organization, established training programs, a journal devoted to the specialty, and inclusion of children's surgery into the curricula of medical schools and general surgical residency programs, another attempt was made to approach the Board for certification.[35] Harvey Beardmore of Montreal (Fig. 1-7), a congenial, diplomatic, and persuasive individual, was chosen as spokesperson. He succeeded where others had failed. In 1973, the ABS approved a new Certificate of Special Competence in Pediatric Surgery to be awarded to all qualified applicants. There was no grandfathering of certification, because all applicants for the certificate had to pass a secured examination administered by the ABS. The first examination was given in 1975 and, for the first time in any specialty, diplomats were required to recertify every 10 years. The accreditation of training programs was moved from the Clatworthy Committee of the AAP, initially, to the APSA Education Committee, and, following Board approval of certification for the specialty, to the Accreditation Council for Graduate Medical Education (ACGME) Residency Review Committee (RRC) for Surgery in 1977.

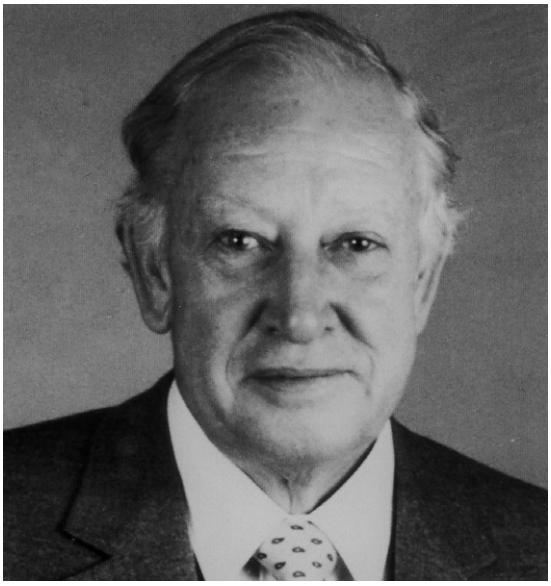


FIGURE 1-7 Harvey Beardmore, distinguished Canadian pediatric surgeon from Montreal.

In 1989, the Association of Pediatric Surgery Training Program Directors was formed and developed as a liaison group with the RRC. Prospective residents applied for postgraduate training in pediatric surgery, initially through a matching process overseen by APSA and, in 1992, through the National Residency Matching Program (NRMP). In 1992, the ABS developed an in-training examination to be given annually to all pediatric surgical residents. In 2000, the ABS approved a separate pediatric surgery sub-board to govern the certification process. By 2010, there were 49 accredited training programs in the United States and Canada. The American College of Surgeons (ACS) recognized pediatric surgery as a separate specialty and developed focused programs at its annual congress devoted to the specialty, including a pediatric surgery research forum. Pediatric surgeons have an advisory committee at the College and have served in leadership positions on numerous committees, the Board of Governors, Board of Regents and as vice-president and president of the College (Kathryn Anderson). At this point pediatric surgery had come of age in North America and the world.

Research

Early research in pediatric surgery was clinical in nature and involved clinical advances in the 1930s and 1940s.[14] Ladd's operation for malrotation in 1936 was a signal event based on anatomical studies.[26] In addition to Gross' work on patent ductus arteriosus and coarctation, Alfred Blalock's systemic-to-pulmonary shunt for babies with tetralogy of Fallot was another landmark. Potts' direct aortic-to-pulmonary artery shunt accomplished similar physiologic results but required

a special clamp. When Potts and Smith developed a clamp with many delicate teeth to gently hold a pulsatile vessel securely, they implemented a major technical advance that enabled the development of vascular surgery.[14] To bridge the gap in long, narrow coarctations of the aorta, Gross devised the use of freeze-dried, radiated aortic allografts and demonstrated their initial effectiveness, further promoting the use of interposition grafts in vascular surgery.[14]

Research in surgical physiology affecting adult surgical patients began to be integrated with research adapted to children. Studies of body composition in injured and postoperative patients by Francis D. Moore in adults were adapted to infants by Rowe in the United States, Peter Rickham and Andrew Wilkinson in the United Kingdom, and Ola Knutrud in Norway. Curtis Artz, John Moncrief, and Basil Pruitt were leaders in adult burn care management, and they stimulated O'Neill's interest in burn and injury research, in children.[14] In 1965, Stanley Dudrick and Douglas Wilmore, working with Jonathan Rhodes in Philadelphia, introduced the use of total parenteral nutrition, first studied in dogs, to sustain surgical patients chronically unable to tolerate enteral feedings, saving countless patients of all ages.[37] Shortly thereafter, Ola Knutrud and colleagues in Norway introduced the use of intravenous lipids. In the 1960s following extensive laboratory studies, Robert Bartlett and Alan Gazzaniga instituted extracorporeal membrane oxygenation (ECMO) for infants with temporarily inadequate heart and lung function, including those with congenital diaphragmatic hernia, certain congenital heart anomalies, meconium aspiration, and sepsis.[38] The technique was subsequently expanded for use in older children and adults. ECMO has been used successfully in thousands of infants and children worldwide.

The field of organ transplantation led by Joseph Murray, Thomas E. Starzl, and Norman Shumway in the United States, Peter Morris and Roy Y. Calne in the United Kingdom, Henri Bismuth and Yann Revillion in France, Jean-Bernard Otte in Belgium, as well as others, provided new options for the treatment of end-stage organ failure in patients of all ages. Renal, liver, and bowel transplantation have significantly altered the outcomes of infants with uncorrectable biliary atresia, end-stage renal disease, short bowel syndrome, and intestinal pseudoobstruction. The use of split liver grafts and living-related donors to offset the problems with organ shortage, has added to the availability of kidneys, liver, and bowel for transplantation, but shortages still exist. Joseph Vacanti and colleagues in Boston and Anthony Atala in Winston Salem have laid the preliminary groundwork for the development of the field of tissue engineering. Using a matrix for select stem cells to grow into various organs, these investigators have successfully grown skin, bone, bladder, and some other tubular organs.

Ben Jackson of Richmond, J. Alex Haller in Baltimore, and Alfred de Lorimier in San Francisco, began experimenting with fetal surgery in the late 1960s and early 1970s.[15] De Lorimier's young associate, Michael Harrison and his colleagues (Scott Adzick, Alan Flake, and others) have provided new insights into fetal physiology and prenatal diagnosis and pursued clinical investigations into the practicalities of intrauterine surgery. Fetal intervention has been attempted for obstructive uropathy related to urethral valves, repair of congenital diaphragmatic hernia, twin–twin transfusion syndrome, arteriovenous shunting for sacrococcygeal teratoma, cystic lung disease, a few cardiac defects, large tumors of the neck, and myelomeningocele repair. Some of these initiatives have been abandoned, but limited protocol-driven investigation continues for fetal myelomeningocele repair in Nashville, Philadelphia, and San Francisco, and fetoscopically placed balloon tracheal occlusion in selected fetuses with diaphragmatic hernia in San Francisco, Providence, and Leuven, Belgium in an attempt to avoid pulmonary hypoplasia.

Patricia Donohoe has carried out fundamental fetal research investigating growth factors that influence embryologic development. Her seminal work defined müllerian inhibitory substance, which influences sexual development and tumor induction. Judah Folkman's discovery of the new field of angiogenesis and antiangiogenesis led him to postulate and search for antiangiogenic agents for use as cancer inhibitors. Antiangiogenic agents are currently being used clinically in a number of cancer protocols for breast and colon cancer, neuroblastoma, gastrointestinal stromal tumors, and others.

Clinical Advances Related to Research

Although many clinical and research accomplishments have occurred in the United States, many related ones have occurred in other parts of the world as more collaborations have developed. However, the United States got a head start on many of these researches, because medical developments were not as hampered during WWII in the United States as in Europe and Asia.

In the late 1960s and early 1970s, the advent of neonatal intensive care units (NICUs) and the evolving subspecialty of neonatology had a major impact on the survival of premature infants and the activities of pediatric surgeons. The first pediatric surgical ICU was established at Children's Hospital of Philadelphia in 1962. Prior to the availability of infant ventilators, monitoring systems, other life support technologies, and microtechniques, most premature infants succumbed. Most infants weighing greater than 1000 g and 75% to 80% weighing greater than 750 g now survive with satisfactory outcomes. With these advances came new challenges in dealing with premature and micropremature surgical patients with immature physiology and conditions previously rarely encountered, such as necrotizing enterocolitis. This led to a universal emphasis on pediatric surgical critical care.

Sophisticated advances in imaging, including computerized tomography (CT), and use of prenatal ultrasound and magnetic resonance imaging to detect anomalies prior to birth and portable sonography for evaluation of cardiac defects, renal abnormalities, and intracranial hemorrhage in the NICU advanced patient care and survival.

The introduction of nitric oxide, surfactant, and newer ventilator technologies, such as oscillating and jet ventilators, have markedly diminished complications and improved outcomes for infants with respiratory distress. Exogenous administration of indomethacin to induce ductus closure and reduce the need for operative intervention has also enhanced survival.

The evolution of comprehensive children's hospitals capable of providing tertiary care to high-risk patients enabled the activities of pediatric surgeons, and this was further amplified by the expansion of specialists in the critical support services of pediatric anesthesia, pathology, and radiology. Other surgical disciplines began to focus their efforts on children, which eventually led to pediatric subspecialization in orthopedics, urology, plastic surgery, otolaryngology, ophthalmology, cardiac surgery, and neurosurgery.

Because it was recognized that trauma was the leading cause of death in children, trauma systems, including prehospital care, emergency transport, and development of assessment and management protocols, were developed by J. Alex Haller, Martin Eichelberger, James O'Neill, Joseph Tepas, and others, dramatically improving the survival of injured children. The implementation of the Glasgow Coma and Pediatric Injury Severity scores aided in triage and outcome research studies. After the initial favorable experience with nonoperative management of splenic injury in children reported by James Simpson and colleagues in Toronto in the 1970s,[39] nonoperative management protocols were applied to blunt injuries of other solid organs, and the availability of modern ultrasound and CT imaging dramatically changed the paradigm of clinical care. A national pediatric trauma database was subsequently developed, which has provided a vital data research base that has influenced trauma care. Criteria for accreditation of level 1 pediatric trauma centers were established through the Committee on Trauma of the ACS to standardize trauma systems and ideal methods of management.

Pediatric surgeons have been intimately involved in collaborative multidisciplinary cancer care for children with solid tumors since the early 1960s. Cooperative cancer studies in children antedated similar efforts in adults by more than 2 decades. In the United States, the National Wilms' Tumor Study, Intergroup Rhabdomyosarcoma Study, Children's Cancer Group, Pediatric Oncology Group and, more recently, Children's Oncology Group are examples. Tremendous strides have been achieved by having access to many children with a specific tumor managed with a standard protocol on a national basis. C. Everett Koop, Judson Randolph, H. William Clatworthy, Alfred de Lorimier, Daniel Hays, Phillip Exelby, Robert Filler, Jay Grosfeld, Gerald Haase, Beimann Othersen, Eugene Weiner, Richard Andrassy, and others represented pediatric surgery on many of the early solid tumor committees. They influenced the concepts of delayed primary resection, second-look procedures, primary reexcision, selective metastectomy, staging procedures, and organ-sparing procedures. Antonio Gentils-Martins in Portugal and Denis Cozzi in Rome have been the leading proponents of renal-sparing surgery for Wilms' tumors.[40] Currently, 80% of children with cancer now survive. The elucidation of the human genome has led to an understanding of genetic alterations in cancer cells and has changed the paradigm of care. Individualized risk-based management, depending on the molecular biology and genetic information obtained from tumor tissue, often determines the treatment protocol and the intensity of treatment for children with cancer.

In addition to the accomplishments noted above, major advances in clinical pediatric surgery, education, and research continue to unfold, and some of these contributions have been extended to adult surgery as well. Examples include the nonoperative management of blunt abdominal trauma, Clatwothy's mesocaval (Clatworthy-Marion) shunt for portal hypertension, and Lester Martin's successful sphincter-saving pull-through procedures for children with ulcerative colitis and polyposis in 1978, all techniques which have been adapted to adults. Jan Louw of Cape Town clarified the etiology of jejunoileal atresia and its management in 1955, and Morio Kasai of Sendai revolutionized the care of babies with biliary atresia by implementing hepatoportoenterostomy in 1955. The latter procedure was implemented in the United States by John Lilly and Peter Altman and in the United Kingdom by Edward Howard, Mark Davenport, and Mark Stringer. Samuel Schuster's introduction of temporary prosthetic coverage for abdominal wall defects; Donald Nuss' minimally invasive repair of pectus excavatum; Hardy Hendren's contributions in managing obstructive uropathy and repair of patients with complex cloaca; Barry O'Donnell and Prem Puri's endoscopic treatment (sting procedure) for vesicoureteral reflux; Mitrofanoff's use of the appendix as a continent catheterizable stoma for the bladder; Joseph Cohen's ureteral reimplantation technique; Malone's institution of the antegrade continent enema (MACE procedure) for fecal incontinence; Douglas Stephen's introduction of the sacroabdominal perineal pull-through for imperforate anus in 1953; Alberto Peña and DeVries' posterior sagittal anorectoplasty in the 1970s; Luis de la Torre's introduction of the transanal pull-through for Hirschsprung disease in the 1990s; laparoscopic-assisted pull-through for Hirschsprung disease and anorectal malformations by Keith Georgeson, Jacob Langer, Craig Albanese, Atsayuki Yamataka, and others; the longitudinal intestinal lengthening procedure by Adrian Bianchi and introduction of the serial transverse enteroplasty (STEP) procedure by H. B. Kim and Tom Jaksic for infants with short bowel syndrome; and use of the gastric pull up for esophageal replacement by Spitz and later Arnold Coran all represent some of the innovative advances in the specialty that have improved the care of children. Early use of peritoneoscopy by Stephen Gans and thoracoscopy by Bradley Rodgers in the 1970s influenced the development of minimally invasive surgery (MIS) in children. Bax, George Holcomb, Craig Albanese, Thom Lobe, Frederick Rescorla, Azad Najmaldin, Gordon MacKinlay, Keith Georgeson, Steven Rothenberg, C. K. Yeung, Jean-Luc Alain, Jean-Stephane Valla, Nguyen Thanh Liem, Felix Schier, Benno Ure, Marcelo Martinez-Ferro, and others have been the early international leaders in pediatric MIS.

CANADA

As events in children's surgery were unfolding in the United States, Canadian pediatric surgery was experiencing a parallel evolution. References have already been made above to some of the clinical and research contributions made in Canada. Alexander Forbes, an orthopedic surgeon, played a leading role at the Montreal Children's Hospital from 1904 to 1929. Dudley Ross was chief-of-surgery at Montreal Children's Hospital from 1937 to 1954 and established the first modern children's surgical unit in Quebec. In 1948, he performed the first successful repair of esophageal atresia in Canada.[41] David Murphy served as chief of pediatric surgery and director of the pediatric surgical training program from 1954 to 1974. He was assisted by Herbert Owen and Gordon Karn, and his first trainee in 1954 was Harvey Beardmore.[42] Beardmore served as chief-of-surgery from 1974 to 1981 and was followed by Frank Guttman from 1981 to 1994 and Jean-Martin Laberge after that. The Sainte-Justine Hospital in Montreal, was founded in 1907. The hospital was combined with the Francophone Obstetrical Unit of Montreal, creating one of the largest maternal/child care centers in North America. Pierre-Paul Collin arrived at the hospital in 1954 after training in thoracic surgery in St. Louis, bringing a commitment to child care. He recruited Jacques Ducharme, who had trained in pediatric surgery in Columbus, Ohio, to join him in 1960. They trained a number of leaders in pediatric surgery in

Canada, including Frank Guttman, Hervé Blanchard, Salam Yazbeck, Jean-Martin Laberge, and Dickens St.-Vil. Jean Desjardins became chief in 1986.

The Hospital for Sick Children in Toronto was established in 1875 by Mrs. Samuel McMaster, whose husband founded McMaster University in Ontario.[42] As was the case in the United States, adult surgeons operated on children in Toronto at the end of the 19th and beginning of the 20th centuries. Clarence Starr, an orthopedic surgeon, was the first chief-of-surgery from 1913 to 1921. W. Edward Gallie served as chief surgeon at the Hospital for Sick Children from 1921 to 1929 and was named chair of surgery at the University of Toronto, where he established the Gallie surgical training program. The Gallie School of Surgery in Canada was compared with that of Halsted at Johns Hopkins in the United States.[42] Because of increasing responsibilities as chair, Gallie relinquished his role as chief of pediatric surgery to Donald Robertson, a thoracic surgeon who held the post until 1944. Arthur Lemesurer, a plastic and orthopedic surgeon became chief and in 1949 began a general pediatric surgical training program that produced Clinton Stephens, James Simpson, Robert Salter, Phillip Ashmore, Donald Marshall, and Stanley Mercer, to name some of the illustrious graduates who became leaders in the field of pediatric surgery in Canada.[14,42] In 1956, Alfred Farmer became surgeon-in-chief at the Hospital for Sick Children and developed several specialty surgical divisions, including one for general pediatric surgery. This allowed for separate specialty leadership under direction of Stewart Thomson from 1956 to 1966. Clinton Stephens was chief from 1966 to 1976 and was ably supported by James Simpson and Barry Shandling. During these 2 decades there was an impressive roster of graduates, including Phillip Ashmore, Gordon Cameron, Samuel Kling, Russell Marshall, Geoffrey Seagram, and Sigmund Ein. The tradition of excellence in pediatric surgery was continued with the appointment of Robert Filler, who arrived from Boston in 1977. Jacob Langer is the current chief of pediatric surgery in Toronto. From the latter three key surgical centers, leadership and progress in pediatric surgery spread across the Canadian provinces with the same comprehensive effect seen in the United States. Colin Ferguson, who trained with Gross in Boston, became chief-of-surgery in Winnipeg. Stanley Mercer began the pediatric surgery effort in Ottawa; there was also Samuel Kling, in Edmonton, where he was joined by Gordon Lees and James Fischer, and Geoffrey Seagram in Calgary. In 1957, Phillip Ashmore was the first trained pediatric surgeon in Vancouver, and he was joined by Marshall and Kliman, who trained at Great Ormond Street. In 1967, Graham Fraser, who also trained at Great Ormond Street joined the Vancouver group and became director of the training program. He was succeeded by Geoffrey Blair. Alexander Gillis trained with Potts and Swenson in Chicago and, in 1961, was the first pediatric surgeon in Halifax, Nova Scotia. He started the training program there in 1988. Gordon Cameron, a Toronto graduate, was the first chief of pediatric surgery at McMasters University in Hamilton. Currently, Peter Fitzgerald is head of the training program in Hamilton, which was approved in 2008.[42] The Canadian Association of Pediatric Surgeons (CAPS) was formed in 1967, three years before APSA, with Beardmore serving as the first president and Barry Shandling as secretary.[43] There are currently eight accredited pediatric surgery training programs in Canada: Halifax, Montreal Children's Hospital, Sainte-Justine Hospital in Montreal, Children's Hospital of Eastern Ontario in Ottawa, Hospital for Sick Children in Toronto, Hamilton, Calgary, Alberta, and Vancouver. All these programs are approved by the Royal College of Surgeons of Canada, and candidates for training match along with the U.S. programs through the NRMP.

UNITED KINGDOM AND IRELAND

In 1852, the Hospital for Sick Children at Great Ormond Street (HSC) opened its doors in a converted house in London.[44] The hospital was the brainchild of Charles West, whose philosophy was that children with medical diseases required special facilities and attention, but those with surgical disorders at the time, mostly trauma related, could be treated in general hospitals.[44] West opposed the appointment of a surgeon to the staff, but the board disagreed and appointed G.D. Pollock. Pollock soon resigned and was replaced by Athol Johnson in 1853. T. Holmes, who followed Johnson, published his 37-chapter book, *Surgical Treatment of the Diseases of Infancy and Childhood,* in 1868.[45] Pediatric care in the 19th century either followed the pattern established in Paris, where all children were treated in hospitals specially oriented toward child care, or the Charles West approach, common in Britain,[46] such as those in Birmingham and Edinburgh, established to provide medical treatment but not surgery for children. In contrast, the Board at the Royal Hospital for Sick Children in Glasgow (RHSC) appointed equal numbers of medical and surgical specialists.[14,47] A major expansion in children's surgery in the latter part of the 19th century followed the development of ether and chloroform anesthesia and the gradual acceptance of antiseptic surgery. Joseph Lister provided the main impetus for antiseptic surgery, which he developed in Glasgow before moving to Edinburgh and then to King's College, London. One of Lister's young assistants in Glasgow was William Macewen, known as the father of neurosurgery, and one of the original surgeons appointed to the RHSC.[14] In Scotland, where pediatric care was generally ahead of the rest of Britain, the Royal Edinburgh Hospital for Sick Children (REHSC) opened in 1860 but did not provide a surgical unit until 1887. The sewing room was used as an operating theater.[48] Joseph Bell, President of the Royal College of Surgeons of Edinburgh, Harold Styles, John Fraser, and James J. Mason Brown, also a president of the Royal College of Surgeons of Edinburgh were the senior surgeons from 1887 to 1964. Gertrude Hertzfeld held a surgical appointment at the REHSC from 1919 to 1947, one of the few women surgeons of that era.[46] In the 19th century, training in pediatric surgery, independent of general surgery in the United Kingdom, occurred in Glasgow. Soon after these hospitals opened, their boards recognized the need for developing dispensaries or outpatient departments. In Manchester, the dispensary actually preceded the hospital. Dispensaries handled many surgical patients, and much of the pediatric surgery of the day was done there. One of the outstanding surgeons of that generation was James Nicoll, who reported 10 years of his work in 1909,[49] one of more than 100 of his publications. He was the "father of day surgery," although only part of his time was devoted to children's surgery because he had a substantial adult practice.[50] He performed pyloromyotomy with success in the late 19th century in a somewhat different fashion from Ramstedt. The Board of the RHSC decided that both physicians or surgeons appointed to the hospital must devote all their professional time to the

treatment of children. In 1919, the University of Glasgow received funding to establish both medical and surgical lectureships, the first academic appointments in Britain. Alex MacLennan was appointed Barclay lecturer in surgical and orthopedic diseases of children at the University of Glasgow from 1919 to 1938. His successor, Matthew White, the Barclay lecturer in 1938, was a thoracic and abdominal surgeon. Mr. Wallace Dennison and Dan Young were among the other surgeons who later filled these posts. In Edinburgh, the children's surgical services and the adult services remained closely associated until Mason Brown became the chief.[14]

Modern pediatric surgery was a development that had to wait until after World War II. Introduction of the National Health Service in Britain, which provided access to care for all citizens, the development of the plastics industry, and many other technical innovations in the mid-20th century, allowed great strides, particularly in neonatal surgery and critical care.[14] In London, and elsewhere in England, general surgeons who were interested in pediatric surgery carried on their pediatric practices in conjunction with their adult practices. Financial considerations influenced their activities, because few were able to earn a living in pediatric surgical practice alone. However, further developments in the specialty were closely related to committed individuals.

Denis Browne, an Australian who stayed in London after serving in WWI, was appointed to the HSC in London in 1924. Browne was the first surgeon in London to confine his practice to pediatric surgery, and he is recognized as the pioneer of the specialty in the United Kingdom.[51–53] He was a tall impressive figure with a somewhat domineering, authoritative manner (Fig. 1-8). Browne's longtime colleague James Crooks called him an "intellectual adventurer, a rebel and a cynic."[51] After World War II, many surgeons from overseas spent time in the United Kingdom; the majority visited the HSC, where they were influenced by Browne. Some subsequently established internationally recognized centers such as Louw in South Africa, and Stephens and Smith in Australia. Browne's major interest was structural orthopedic anomalies, and as an original thinker, he achieved widespread recognition for promoting intrauterine position and pressure as a cause of these deformities.[53] He developed instruments, retractors, and splints to assist in his work, all named after himself. His early contemporaries were L. Barrington-Ward and T. Twistington Higgins, surgeons of considerable stature. It was Higgins who initially held discussions in London that led to the formation of the British Association of Pediatric Surgeons (BAPS) in 1953. Browne became the association's first and longest-serving president. The Denis Browne Gold Medal, an award given by the BAPS, remains a symbol of his presence and demonstrates his views (Fig. 1-9). In his later years in the National Health Service, his colleagues included George McNab, introducer of the Holter valve for hydrocephalus; David Waterston, an early pediatric cardiothoracic surgeon; and David Innes Williams, doyen pediatric urologist of Britain.[14] Each of these outstanding men made major contributions to the development of pediatric surgery. Many young surgeons continued to flock to HSC in London for training in pediatric surgery, including Nate Myers, Barry O'Donnell, H.H. Nixon and others. Andrew Wilkinson replaced Browne as surgeon-in-chief. Many other developments were also taking place. Wilkinson in London and Knutrud in Oslo were studying infant metabolism. Isabella Forshall, later joined by Peter Rickham, established an excellent clinical service in Liverpool. She was one of the few female pediatric surgeons of the time and was president of the BAPS in 1959. Pediatric surgery services were established in Sheffield by Robert Zachary, and in Manchester, Newcastle, Birmingham, Southampton, Bristol, Nottingham, and Leeds. Lewis Spitz from South Africa trained at Alder Hey Hospital in Liverpool with Peter Rickham in 1970. After a brief stay in Johannesburg, he immigrated to the United Kingdom to work with Zachary in Sheffield in 1974. He was then named the Nuffield Professor and head at Great Ormond Street, London and provided excellent leadership and strong surgical discipline at the HSC, leading by example for many years, until 2004 when he retired. His main areas of expertise included esophageal surgery, congenital hyperinsulinism, and separation of conjoined twins.[54,55] His colleagues included Kiely, Brereton, Drake, and Pierro. The latter established a strong research base at the institution and succeeded Spitz as the Nuffield Professor.

FIGURE 1-8 Sir Denis Browne, London, United Kingdom.

IRELAND

In 1922, Ireland was divided into six northern counties under British rule and 26 southern counties that became the Republic of Ireland. The first children's hospital in Ireland was in the south, the National Children's Hospital, opening on Harcourt Street in Dublin in 1821.[56] The Children's University Hospital in Dublin was founded on Temple Street in 1872. John Shanley, a general surgeon, was appointed to the Temple Street facility and devoted all his surgical activities to children. Another general surgeon, Stanley McCollum, worked at the National Hospital and did pediatric surgery at the Rotunda at the Maternity Hospital. A third children's hospital, Our Lady's Hospital for

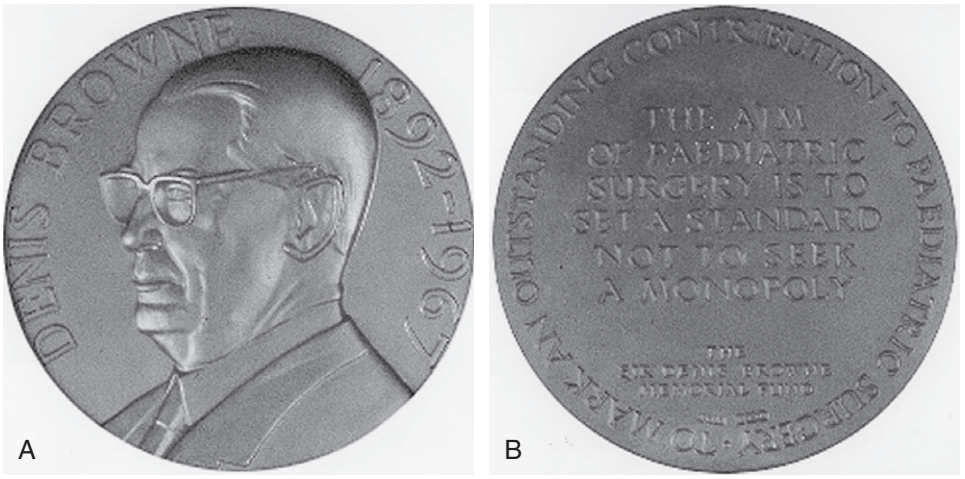


FIGURE 1-9 Denis Browne Gold Medal. **A,** Front of the medal. **B,** Back of the medal, which reads, "The aim of paediatric surgery is to set a standard not to seek a monopoly."

Sick Children, managed by the Daughters of Charity of St. Vincent De Paul, opened in 1956 in Crumlin. Barry O'Donnell was the first full-time, fully trained pediatric surgeon at this facility. Each of the children's hospitals had an academic affiliation, the National Hospital with Trinity College, and Temple Street and Our Lady's with The Royal College of Surgeons University College. Edward Guiney was added to the consultant staff of Our Lady's in 1966 and also was appointed to Temple Street and assisted McCollum at the National Children's Hospital, Dublin. From 1979 to 1993, Ray Fitzgerald, Prem Puri, and Martin Corbally were added as consultant pediatric surgeons. Following Barry O'Donnell's retirement in 1991 and Guiney stepping down in 1993, Fergal Quinn was eventually named to replace him. The Children's Research Center was developed in 1971, with Guiney appointed as director in 1976. He was replaced by Prem Puri, who has mentored numerous overseas research fellows and provided outstanding research concerning many neonatal and childhood conditions. O'Donnell conceived and Puri developed the innovative sting procedure to endoscopically treat vesicoureteral reflux, initially by Teflon injection and subsequently with Deflux. O'Donnell, Guiney, and Fitzgerald have served as presidents of the BAPS. Both O'Donnell and Puri are Denis Browne Gold Medal recipients and achieved international stature. Fitzgerald was president of European Pediatric Surgeons Association (EUPSA) and IPSO, and O'Donnell was president of the Royal College of Surgeons of Ireland. Puri served as president of EUPSA and the WOFAPS (World Federation of Associations of Pediatric Surgeons)

Pediatric surgery in Northern Ireland developed more slowly. Brian Smyth, who trained at Great Ormond Street and Alder Hey Hospitals, was appointed the first specialist pediatric surgeon consultant in 1959. He was joined by a Scotsman, William Cochran, who trained in Edinburgh. Following training in Newcastle and Cape Town, Victor Boston was added as a pediatric surgery consultant in 1975. Political unrest and economic constraints placed some limitations on growth in the north. Cochran returned to Scotland, and in 1995, McCallion was added as a consultant. Today they have similar standards to the southern centers in Ireland.

EUROPE

Europe served as the cradle of pediatric surgery, but because of space limitations, only the major developments and leading figures can be discussed. In France, the Hôpital des Enfants Malades has a long and storied history, starting with the contributions of Guersant, Giraldes, and de Saint-Germain from 1840 to 1898.[57] Most of their work involved orthopedic conditions and the management of infectious problems. Kirmisson, also well-versed in orthopedic disorders, was appointed the first professor of pediatric surgery in 1899 and published a pediatric surgical textbook in 1906 that contained radiologic information and discussed osteomyelitis and some congenital anomalies. In 1914, Broca described the management of intussusception, instances of megacolon, and experience with Ramstedt's operation for pyloric stenosis. He was succeeded by Ombredanne, a self-taught pediatric surgeon whose works were published by Fevre in 1944.[58] Petit performed the first successful repair of type C esophageal atresia in France in 1949. Because of two world wars, intervals of foreign occupation, and long periods of recovery in all of Europe, it was some time after WWII before modern pediatric surgery could develop in this part of the world. Following WWII, Bernard Duhamel was at the Hôpital des Enfantes Malades but moved to St. Denis, where he devised the retrorectal pull-through for Hirschsprung disease, an alternative procedure to the Swenson operation in 1956 (Fig. 1-10).[59] He was the first editor of *Chirurgie Pediatrique,* started in 1960. Denys Pellerin became chief-of-surgery at the Hôpital des Enfantes Malades and developed a strong department at the institution until he retired in 1990. His successor was Claire Nihoul-Fekete, the first female professor of pediatric surgery in France. Fekete was recognized for her stylish demeanor and expertise in intersex surgery, esophageal anomalies, and congenital hyperinsulinism. She was succeeded by Yann Revillion, an international leader in intestinal transplantation. Yves Aigran plays a leadership role as well. Elsewhere, Michel Carcassone, who developed pediatric surgery in Marseille, had expertise in treating portal hypertension and was an early advocate of a primary pull-through procedure for Hirschsprung disease. He also served as the

FIGURE 1-10 Bernard Duhamel, Paris, France.

editor-for-Europe for the *Journal of Pediatric Surgery*. J.M. Guys is currently chief in Marseilles. Prevot was the first leader in Nancy. The Société Francaise de Chirurgie Infantile was established in 1959, with Fevre as the first president. The group changed its name to the French Society of Pediatric Surgery in 1983. A strong pediatric oncology presence has existed in Villejuif for many years, initially under the direction of Mme. Odile Schwiesgut.

Pediatric surgical development in Scandinavia also has a rich history. In Sweden, The Princess Lovisa Hospital in Stockholm opened in 1854, but it was not until 1885 that a surgical unit was added under the direction of a general surgeon.[60,61] The first pediatric surgery unit was actually started at the Karolinska Hospital in 1952 and was transferred to St. Gorans Hospital in 1982. In 1998, all pediatric surgery in Stockholm was moved to the newly constructed Astrid Lindgren Children's Hospital at Karolinska University. Three other major pediatric surgery centers were developed in Gothenberg, Uppsala, and Lund. Philip Sandblom was appointed chief-of-surgery at Lovisa from 1945 to 1950, and then he moved to Lund and, later, Lausanne as chief-of-surgery. He was succeeded by Theodor Ehrenpreis, who moved to the Karolinska Pediatric Clinic in 1952. He had a strong interest in research in Hirschsprung disease. Gunnar Ekstrom took his place, and he was succeeded by Nils Ericsson, whose major interest was pediatric urology. Bjorn Thomasson became chief at St. Gorans in 1976. Tomas Wester is the current chief in Stockholm. Gustav Peterson was the initial chief of pediatric surgery in Gothenberg. Ludvig Okmian became the chief of pediatric surgery in Lund in 1969 and helped develop the infant variant of the Engstrom ventilator, and along with Livaditis, employed circular myotomy for long gap esophageal atresia. In 1960, Gunnar Grotte was appointed the first chief of pediatric surgery in Uppsala. He was joined by Leif Olsen, and their major interests included pediatric urology, Hirschsprung disease, and metabolism. The Swedish Pediatric Surgical Association was formed in 1952, and Swedes also participate in the Scandinavian Association of Pediatric Surgeons, founded in 1964.

In Finland, pediatric surgery developed after WWII. Mattie Sulamaa, the pioneer in Finland, was the first to work in the new children's hospital in Helsinki, which opened in 1946. He was instrumental in introducing pediatric anesthesiology. He trained young students, who later started programs at children's hospitals in Turku and Oulu, and university centers in Tampere and Kuopio. He retired in 1973 and was succeeded by Ilmo Louhimo, who specialized in cardiothoracic surgery. He trained Harry Lindahl and Risto Rintala. Rintala is the current chief at Helsinki Children's Hospital and is well recognized for his expertise in pediatric colorectal surgery. Lindahl is a leader in upper gastrointestinal surgery, endoscopy, and the management of esophageal atresia.

There were no children's hospitals in Norway. However, pediatric surgery was strongly influenced by Ola Knutrud of Oslo, beginning in 1962 when he was appointed chief of pediatric surgery at the University Rikshospital. He was an early leader in the field, with interest in pediatric fluid and electrolyte balance, metabolism, fat nutrition, and congenital diaphragmatic hernia. In 1975, Torbjorn Kufaas was named chief of pediatric surgery at the University Hospital in Trondheim.

In Denmark, the first children's hospital opened in1850 and moved to a new facility named after Queen Louise in 1879, with Harald Hirschsprung, a pediatrician appointed as chief physician. Hirschsprung's interests centered on surgical problems, including esophageal atresia, intussusception, ileal atresia, pyloric stenosis, and congenital megacolon.[62] C. Winkel Smith and Tyge Gertz initiated pediatric surgery at University Hospital in Copenhagen, with the latter performing the first successful repair of esophageal atresia in Denmark in 1949. Smith mysteriously disappeared in 1962 but was not declared deceased until 1968.[63] Knud Mauritzen was named his successor as director of pediatric surgery in Copenhagen. Ole Nielsen, a urologic surgeon, succeeded him. Carl Madsen became consultant surgeon at Odense University Hospital; however, there is no department of pediatric surgery there or in Arhus, where pediatric urology and children's surgery are performed in the Department of Urology or Surgery. The only Danish department of pediatric surgery exists in Copenhagen. Although the Danish governmental specialty rules listed pediatric surgery as a specialty in 1958, this was rescinded in 1971 and has not been restored.[63]

Modern pediatric surgery in Switzerland starts with the pioneer in that country, Max Grob. A native of Zurich, he trained in general surgery with Clairmont in Zurich in 1936 and then spent 6 months in Paris at the Hôpital des Enfantes Malades under Ombredanne. He returned to Zurich and entered private practice. It was during WWII that he was appointed to replace Monnier, a general surgeon in charge at the Children's Hospital, whom he met during training. His pediatric surgical practice was quite varied and included plastic surgery and cardiac surgery.[64] He modified Duhamel's operation for Hirschsprung disease and did the first hiatal hernia repair in a child in Switzerland. He trained a new generation of pediatric surgeons in Zurich, including Marcel Bettex, Noel Genton, and Margrit Stockman. The Swiss Society of Pediatric Surgery was formed in 1969, with Grob as its first president.[65] Peter Paul Rickham moved from Liverpool to succeed Grob in Zurich in 1971. Marcel Bettex

developed a separate department of pediatric surgery in Bern, as did Noel Genton in Lausanne, Alois Scharli in Luzern, Anton Cuendet in Geneva, and Nicole in Basel. Urs Stauffer replaced Professor Rickham as chief in Zurich in 1983. Martin Meuli is the current chief in Zurich. Claude Lecoutre succeeded Cuendet in Geneva. The current chief there is Barbara Wildhaber. Peter Herzog is presently chief in Basel, Marcus Schwoebel in Lausanne, and Zachariah Zachariou in Bern. Alois Scharli began the journal *Pediatric Surgery International* in 1985 and served as editor-in-chief for 18 years, followed by Puri and Coran as the current co–editors-in-chief.

In Germany, pediatric care began with the development of children's hospital facilities in various cities across the country, most notably, in Munich, Cologne, and Berlin. Early contributions from Max Wilms in Liepzig and Conrad Ramstedt in Münster have been previously noted.[17,20] Progress was somewhat hampered by war, political and social unrest, and the separation of the country into East Germany and West Germany during the occupation following WW II. Children's surgical units developed either in university settings within adult hospitals or in independent children's hospitals. The contributions of Anton Oberniedermayr and Waldemar Hecker in Munich, who was the first professor of pediatric surgery in the Federal Republic of Germany, Fritz Rehbein in Bremen, and Wolfgang Maier in Kahrlsruhe are well recognized.[66] Fritz Rehbein's clinic in Bremen attracted many young men to train there. He was a thoughtful and resourceful pediatric surgical leader who contributed much to patient care, including the Rehbein strut for pectus excavatum, modifications in esophageal surgery, low pelvic anterior resection for Hirschsprung disease (the Rehbein procedure),[67,68] and a sacral approach with rectomucosectomy of the atretic rectum with abdominoperineal pull-through for high imperforate anus (Fig. 1-11). He was a founding editor of *Zeitschrift Kinderchirurgie* in 1964, which was the precursor of the *European Journal of Pediatric Surgery* following merger with the French journal *Chirurgie Pedaitrique* in 1990. Alex Holschneider was editor from 1980 to 2007, and Benno Ure of Hannover has been the editor-in-chief since 2007. Many of Rehbein's trainees went on to leadership roles in other European cities, including Michael Hoellwarth (Graz), Alex Holschneider (Cologne), Pepe Boix-Ochoa (Barcelona), and others. He was recognized throughout Europe as a leader in the field and was a recipient of the Denis Browne Gold Medal from the BAPS and many other awards. His contributions to European pediatric surgery are recognized by the establishment of the Rehbein Medal, awarded each year by the EUPSA, representing 28 countries in Europe. In West Germany, pediatric surgery was not recognized as an independent specialty until 1984. Following the fall of the Berlin Wall and the reunification of Germany in 1990, the 33 East German pediatric surgery programs joined those of the West from the Federal Republic of Germany and formed a joint German Society of Pediatric Surgery.

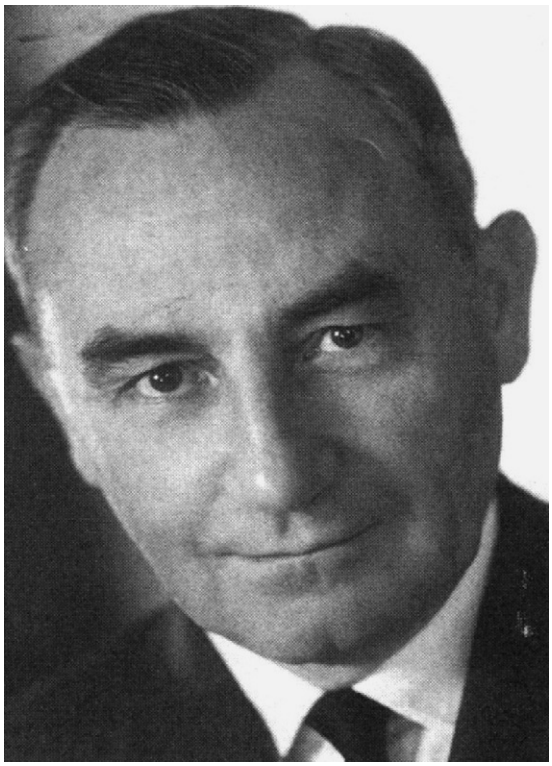


FIGURE 1-11 Fritz Rehbein, Bremen, Germany.

In Italy, early evidence of a hospital devoted to children dates back to the 15th century with the Hospital of the Innocents in Florence, which was more of a foundling home than a hospital. Other facilities for sick children were documented in the 1800s in many Italian cities. The first hospital dedicated to children's surgery was in Naples in 1880. In Milan in 1897, Formiggini was the surgeon-in-charge, and he eventually started the first Italian pediatric surgical journal, *Archivio di Chirurgia Infantile,* in 1934. It was a short-lived effort, however. Once again WW II delayed progress. Carlo Montagnani spent 18 months in Boston in 1949 and returned to Florence, where he translated Gross' textbook into Italian. He had a productive career as a pioneer pediatric surgeon. He organized the Italian Society of Pediatric Surgery in 1964, with Pasquale Romualdi of Rome serving as the first president. That was the same year Franco Soave of Genoa described the endorectal pull-through for Hirschsprung disease (Fig. 1-12). In 1992, the Italian journal ceased to publish, and the *European Journal of Pediatric Surgery* became the official journal of the Italian Society. Major advances in the management of neonatal conditions, childhood tumors, Hirschsprung disease, esophageal disorders, and pediatric urology have emanated from Italy in the past 2 decades from centers in Rome, Milan, Genoa, Naples, Pavia, Florence, Bologna, Turin, and others.

In the Netherlands, the first children's hospital was opened in Rotterdam in 1863, with eight beds located in a first-floor apartment. The children's hospital in Amsterdam followed in 1865 in an old orphanage. In 1899, the name of the facility was changed to Emma Children's Hospital, after the Queen. Volunteer adult surgeons did whatever children's surgical work that presented. Throughout the rest of the 19th century, additional children's facilities sprung up in other cities. R.J. Harrenstein was the first full-time surgeon appointed at the Emma Children's Hospital. In the 1970s, Born at The Hague and David Vervat in Rotterdam dedicated themselves to children's care. Vervat was also an early editorial consultant for the *Journal of Pediatric Surgery.* Jan Molenaar trained with Vervat and eventually replaced him at Erasmus University in Rotterdam in 1972. Molenaar served as the editor-for-Europe for the *Journal of Pediatric Surgery.* Franz Hazebroeck replaced Molenaar as chief in 1998, and Klaas Bax subsequently succeeded Hazebroeck. The Rotterdam school focused on basic

FIGURE 1-12 Franco Soave, Genoa, Italy.

science research and a high level of clinical care. Anton Vos spent time in Boston with Gross and Folkman and later returned to Amsterdam as an associate of Professor Mak Schoorl. In 1991, he was appointed professor of pediatric surgery at the University of Amsterdam with a strong focus on pediatric oncology. Hugo Heij succeeded Vos as chief in 1999. Currently there are five pediatric surgery training programs in the Netherlands located in Rotterdam, Amsterdam, Utrecht, Nijmegen, and Groningen. Trainees are certified by the European Board of Pediatric Surgery (EBPS), sponsored by the Union of European Medical Specialties (EUMS).

In Spain, the modern day pioneers included Julio Monoreo, who was appointed the first head of pediatric surgery at the Hospital of the University of La Paz, Madrid in 1965. Pepe Boix-Ochoa filled the same role at Hospital Valle de Hebron in Barcelona. Juan Tovar succeeded Monoreo after his passing. In the 1970s and 1980s, major regional pediatric surgical centers were located in numerous cities around the country. The Spanish Pediatric Surgical Association was formed as an independent group for pediatrics in 1984. Tovar is the current editor-for-Europe for the *Journal of Pediatric Surgery* and served as president of EUPSA.

Other leaders in Europe included Aurel Koos, Imre Pilaszanovich, and Andras Pinter in Hungary; Petropoulos, Voyatzis, Moutsouris Pappis, and Keramidis in Greece; Kafka, Tosovsky, and Skaba in the Czech Republic; Kossakowski, Kalicinski, Lodzinski, and Czernik in Poland; and Ivan Fattorini in Croatia. In Austria, the leaders in the field included Sauer and Hoellwarth in Graz, Rokitansky and Horcher in Vienna, Menardi in Innsbruck, Oesch in Salzburg, and Brandesky in Klangenfurt. In Turkey, Ihsan Numanoglu developed the first pediatric surgery service in Izmir in 1961. Akgun Hiksonmez started the program at Hacettepe University in Ankara in 1963. Acun Gokdemir was an early pediatric urologist in Istanbul. Daver Yeker, Cenk Buyukunal, Nebil Buyukpamukcu, and Tolga Dagli are major contributors to contemporary Turkish pediatric surgery and urology. The Turkish Association of Pediatric Surgeons (TAPS) formed in 1977, with Hicsonmez elected the first president.

AUSTRALIA AND NEW ZEALAND

The first children's hospital opened in Melbourne, Australia in 1870.[69] In 1897, Clubbe performed a successful bowel resection for intussusception in Sydney. In 1899, Russell published the method of high ligation of an inguinal hernia sac. Hipsley described successful saline enema reduction of intussusception in 1927. As was the case elsewhere, pediatric surgery did not experience significant growth until after WW II. Howard performed the first successful repair of esophageal atresia in Melbourne in 1949. He was joined there by F. Douglas Stephens, who had spent time with Denis Browne in London, and he directed the research program at the Royal Melbourne Children's Hospital for many years. Bob Fowler and Durham Smith later joined the Melbourne group. They set a standard for investigation of malformations of the urinary tract and anorectum. Stephens developed the sacroperineal pull-through operation for high anorectal malformations. The pediatric surgery staff in Melbourne was exemplary and added Nate Myers, Peter Jones, Alex Auldist, Justin Kelley, Helen Noblett, and Max Kent to the group. Archie Middleton, Douglas Cohen, and Toby Bowring led the way in Sydney, Geoff Wylie in Adelaide, Alastair MacKellar in Perth, and Fred Leditschke in Brisbane.

Pediatric surgical contributions from Australia were considerable. Myers was an expert in esophageal atresia and provided the first long-term outcome studies.[70] Noblett promoted nonoperative gastrografin enema for simple meconium ileus and devised the first forceps for submucosal rectal biopsy for Hirschsprung disease.[71,72] Jones spearheaded the nonoperative management of torticollis and management of surgical infections. Fowler devised the long-loop vas operation for high undescended testis[73]; MacKellar instituted the first trauma prevention program; Kelly developed a scoring system for fecal incontinence and total repair of bladder exstrophy; and Smith and Stephens developed the Wingspread classification for anorectal malformations. Hutson's studies on the influence of hormones and the genitofemoral nerve on testicular descent and colonic motility, Cass' insights into the genetics of Hirschsprung disease, and Borzi and Tan's leadership in pediatric MIS are more recent examples of Australian contributions to the field. Pediatric surgery in New Zealand took longer to develop. There are now four major training centers in Auckland, Hamilton, and Wellington on the North Island and Christchurch on the South Island. Leaders include Morreau in Auckland, supported by Stuart Ferguson and others; Brown in Hamilton; Pringle in Wellington; and Beasley in Christchurch. A significant outreach program for the islands of the South Pacific is in place.

ASIA

There have been significant contributions to pediatric surgery from Japan, China, Taiwan, and other Asian countries following WW II. In China, Jin-Zhe Zhang in Beijing survived war,

national turmoil, and the Cultural Revolution to emerge as that nation's father figure in children's surgery. Other early leaders included She Yan-Xiong and Ma in Shanghai and Tong in Wuhan. The latter was the first editor of the *Chinese Journal of Pediatric Surgery*. The first pediatric surgery congress in China was held in 1980, and the China Society of Pediatric Surgeons was formed in 1987. There is a new generation of pediatric surgeons, including Long Li, G-D Wang, and others. Major children's hospitals are now located in Beijing, Shanghai, Fudan, Shenyang, Wuhan, and many other mainland cities. The use of saline enemas under ultrasound guidance, as well as the introduction of the air-enema for reduction of intussusception, are examples of significant Chinese contributions. Paul Yue started the first pediatric surgery unit in Hong Kong in 1967. H. Thut Saing was appointed the first chair of pediatric surgery at the University of Hong Kong in 1979.[74] Paul Tam and CK Yeung trained with Saing and went on to have very productive careers. Tam spent time at Oxford in the United Kingdom and returned to become chair of pediatric surgery at the University of Hong Kong in 1996. Yeung succeeded Kelvin Liu as chief of pediatric surgery at the Chinese University Prince of Wales Hospital. Both Tam and Yeung provided pediatric surgery leadership in Hong Kong and have been productive in the study of the genetic implications of many surgical disorders, including Hirschsprung disease and neuroblastoma (Tam) and application of MIS, particularly in pediatric urology (Yeung).

V.T. Joseph was the first director of pediatric surgery in Singapore in 1981. Following his departure, Anette Jacobsen has been influential in further developing the specialty and providing strong leadership in children's surgery in Singapore.[74] Sootiporn Chittmittrapap, Sriwongse Havananda, and Niramis have been strong advocates in establishing a high level of pediatric surgical care in Thailand. In Vietnam, years of political strife and conflict delayed progress in children's surgery. Nguyen Thanh Liem has emerged as a leading contributor from Hanoi, with extensive experience in the use of MIS for managing a myriad of pediatric surgical conditions. There are now 13 pediatric surgical centers in Vietnam.[74]

In Japan, the first generation of pediatric surgeons appeared in the early 1950s: Ueda in Osaka, Suruga at Juntendo University in Tokyo, Kasai at Tohoku University in Sendai, and Ikeda at Kyushu University in Fukuoka. Suruga performed the first operation for intestinal atresia in 1952. Kasai performed the first hepatoportoenterostomy for uncorrectable biliary atresia in 1955 (Fig. 1-13), and Ueda performed the first successful repair of esophageal atresia in 1959.[14] The first children's hospital in the country was the National Children's Hospital in Tokyo, opened in 1965. The first department of pediatric surgery was established at Juntendo University in Tokyo in 1968 by Suruga (Fig. 1-14); 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 include Okamoto and Okada in Osaka; Nakajo, Akiyama, Tsuchida, and Miyano in Tokyo; Ohi and Nio in Sendai; Suita in Fukuoka and Ken Kimura in Kobe and later in Iowa and Honolulu. These individuals made seminal contributions in the fields of nutrition, biliary and pancreatic disease, management of choledochal cyst, oncology, and intestinal disorders, including Hirschsprung disease, esophageal atresia, duodenal atresia, and tracheal reconstruction. In recent decades, laboratories and clinical centers in Asia, particularly in Japan and Hong Kong, have generated exciting new information in the clinical and basic biological sciences that continues to enrich the field of children's surgery.

FIGURE 1-13 Morio Kasai, Sendai, Japan.

FIGURE 1-14 Keijiro Suruga, Tokyo, Japan.

DEVELOPING COUNTRIES

Nowhere in the world is the global burden of surgical disease more evident than in Africa. Pediatric surgery in underdeveloped areas of the world suffers from a lack of infrastructure, financial resources, and governmental support. In Africa, hepatitis B, malaria, malnutrition, human immunodeficiency virus–acquired immune deficiency virus (HIV-AIDS), and the ravages of political unrest and conflict play a major role in the higher childhood mortality noted on the continent. There are some exceptions, such as South Africa, where pediatric surgery is an established specialty with major children's centers in Cape Town, Johannesburg, Durban, Pretoria, and Bloemfontein; in Egypt with centers in Cairo and Alexandria; and in Nairobi, Kenya. The pioneer pediatric surgeon in South Africa was Jan Louw of Cape Town (Fig. 1-15). Collaborating with Christian Barnard in 1955, they demonstrated, in a fetal dog model, that most jejunoileal atresias were related to late intrauterine vascular accidents to the bowel and/or mesentery. Sidney Cywes succeeded Louw at the Red Cross Memorial Children's Hospital in 1975. He was the first surgeon in the country to limit his practice to children.

Cywes was joined in Cape Town by Michael Davies, Heinz Rode, Alastair Millar, Rob Brown, and Sam Moore. Millar is the current surgeon-in-chief. Michael Dinner was the first professor of pediatric surgery at Witwatersrand University in Johannesburg. Derksen and Jacobs started the pediatric surgery service in Pretoria and were succeeded by Jan Becker in 1980. R. Mikel was the first professor of pediatric surgery at the University of Natal in Durban; he was succeeded by Larry Hadley. The South African Association of Pediatric Surgeons was formed in 1975, with Louw serving as its first president.[75] Major contributions to pediatric surgical care from South Africa include management of intersex, separation of conjoined twins, childhood burn care, pediatric surgical oncology, treatment of jejunoileal atresia, caustic esophageal injury, Hirschsprung disease, and liver transplantation. In 1994 in Nairobi, where pediatric surgery was pioneered by Julius Kyambi, the Pan African Pediatric Surgical Association (PAPSA) was established with pediatric surgeons from all the nations on the continent joining as members.

FIGURE 1-15 Professor Jan Louw, Cape Town, South Africa.

In India, the Association of Indian Surgeons first recognized pediatric surgery as a separate section in 1964. This organization subsequently became independent as the Indian Association of Pediatric Surgeons (IAPS) and met for the first time in New Delhi in 1966. Facilities for pediatric surgical care were limited to a few centers in metropolitan areas. Early leaders in the field included S. Chatterjee, R.K. Ghandi, P. Upadhaya, R.M. Ramakrishnan, V. Talwalker, and S. Dalal. Ms. Mridula Rohatgi was the first female professor of pediatric surgery. Professor Ghandi served as president of the WOFAPS, and presently, Professor Devendra Gupta of New Delhi is the president-elect of that organization. There are currently 24 pediatric surgery teaching centers in the country, all located in major cities. Rural care is still less than desirable, and there are only 710 pediatric surgeons to care for a population of 1.2 billion people.

Space limitations prevent individual mention of some other countries and deserving physicians who have made contributions to the field of pediatric surgery.

The discipline of pediatric surgery around the world is mature at this point and as sophisticated as any medical field. It has become a science-based enterprise in a high-technology environment. In the developed world, children with surgical problems have never been as fortunate as now. Pediatric surgery has truly become internationalized, with various countries developing national societies and striving to improve the surgical care of infants and children. The availability of the Internet to rapidly disseminate information has provided a method to share knowledge and information regarding patient care. The World Federation of Associations of Pediatric Surgeons (WOFAPS), which originated in 1974 and under the leadership of Professor Boix-Ochoa, the organization's secretary general, has grown and matured as an organization that now comprises more than 100 national associations.[76] It is an international voice for the specialty and sponsors a world congress of pediatric surgery every 3 years in a host country and provides education, support, and assistance to underdeveloped countries to improve the surgical care of infants and children. With children representing a higher percentage of the population in the developing world, this becomes an increasingly important factor in enhancing the global effort to provide better surgical care for children.

The complete reference list is available online at www.expertconsult.com.

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[1] to 12,000 in 2010, documenting the acceleration of knowledge of human genetics. 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, until recently there was 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 had 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,[2] 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. 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, whereas 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.[3–5] Numerous disorders that were initially 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 cause but require the synergistic action of mutant alleles at

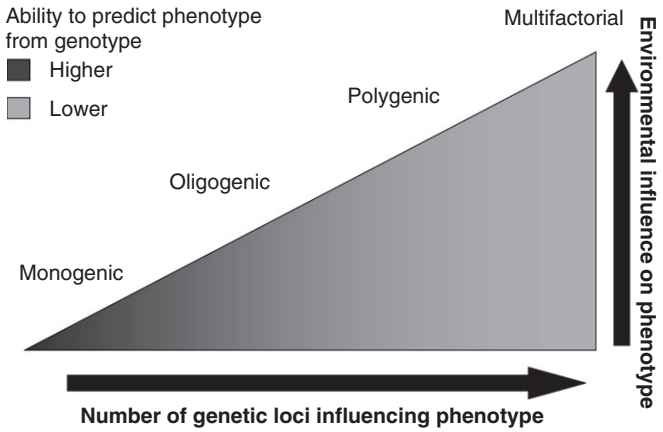


FIGURE 2-1 Conceptual continuum of modern molecular genetics. The genetic characterization of a disorder depends on (1) whether a major locus makes a dominant contribution to the phenotype, (2) the number of loci that influence the phenotype, and (3) the presence and extent of environmental influence 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.

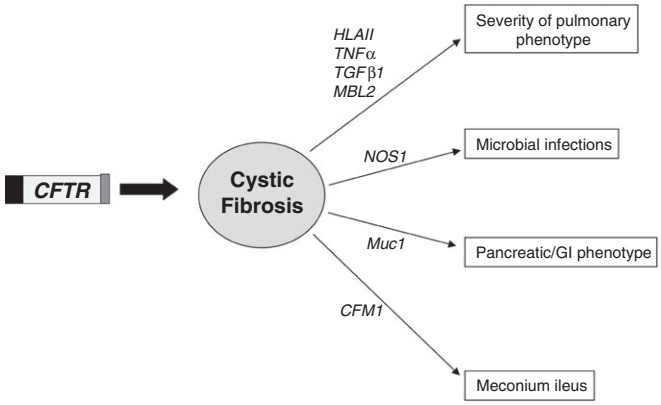


FIGURE 2-2 Complexity in monogenic diseases. Mutations in the *cystic fibrosis transmembrane conductance regulator* (*CFTR*) almost always cause the cystic fibrosis (CF) phenotype. Owing to modification effects by other genetic factors, the presence and nature of mutations at the *CFTR* locus cannot 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; *TGFB1*, transforming growth factor-β1; *TNF*, tumor necrosis factor encoding gene.

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 the 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.[6] Once the *CFTR* gene was cloned,[7] 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 patients with CF. 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.[8–10] 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.[11,12] Further phenotypic analysis led to the discovery of several other loci linked to phenotype, including (1) the association of low-expressing mannose-binding lectin (*MBL2*; previously known as *MBL*) alleles, human leukocyte antigen (HLA) class II polymorphisms, and variants in tumor necrosis factor-α (*TNFA*) and transforming growth factor-β1 (*TGFB1*) with pulmonary aspects of the disease;[13–16] (2) the correlation of intronic nitric oxide synthase 1 (*NOS1*) polymorphisms with variability in the frequency and severity of microbial infections[17]; and (3) the contribution of mucin 1 (*Muc1*) to the gastrointestinal aspects of the CF phenotype in mice (Fig. 2-2).[18] 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.[19] Second, and perhaps more surprising, a study group 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 a requisite for the development of CF might not be true.[20] Identification of these and many other gene modifiers and appreciation of their importance in this and other diseases is a major step forward. Although at the present time, the effects of these polymorphisms are incompletely understood, such findings could lead to potential therapeutic targets for CF or identification of risk factors early in life.

Oligogenic Disorders

Recent developments in defining the molecular genetics of Hirschsprung disease (HD) exemplify a relatively new concept in genetics—the oligogenic disorder. Although mathematic analyses of oligogenicity are beyond the scope of this discussion,[21,22] 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.[23,24] So far a combination of linkage, positional cloning studies, and functional candidate gene analyses has identified eight HD genes (Table 2-1),[25] of which the proto-oncogene *RET* is thought to be the main predisposing locus,[26,27] particularly in families with a high incidence of L-HD.[28]

The non-mendelian 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 chromosome 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 chromosome 9q31 was detected when families with potentially weak *RET* mutations were analyzed independently,[27] 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 that 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.[28]

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, which is a first step toward identifying their underlying genes. More important, the establishment of non-mendelian 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 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.[29] However this risk is considerably less than would be predicted based on mendelian patterns of inheritance.[30] In addition, HPS has been reported as an associated feature in multiple defined genetic syndromes[31–35] and chromosomal abnormalities[36–40] and anecdotally with many other defects,[41–45] 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 (*NOS1*) within the pyloric muscle.[46] A detailed analysis of the molecular mechanisms of this alteration has been published, describing a reduction of messenger RNA (mRNA) expression of *NOS1* exon 1c, with a compensatory up-regulation of *NOS1* exon 1f variant mRNA in HPS.[46] DNA samples of 16 HPS patients and 81 controls were analyzed for *NOS1* 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

TABLE 2-1

Genes Associated with Hirschsprung Disease and Relationship to Associated Anomalies

Gene	*Gene Locus*	*Gene Product*	*Inheritance*	*Population Frequency (%)*	*Associated Anomalies*	*Incidence in Gene 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
NRTN	19p13.3	Ligand for *RET* and *GFRα-2*	AD	<1*	Unknown	—
GFRA1	10q26	Coreceptor for *GDNF*	Unknown	†	Unknown	—
EDNRB	13q22	Receptor for *EDN3*	AD/AR	3-7	Waardenburg syndrome	Unknown
EDN3	20q13.2-13.3	Ligand for *EDNRB*	AD/AR	5	CCHS Waardenburg syndrome	1.8-1.9 Unknown
ECE1	1p36.1	*EDN3* processing gene	AD	<1	Unknown	—
SOX10	22q13.1	Transcription factor	AD	<1	Waardenburg 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); *ECE1*, endothelin-converting enzyme-1; *EDNRB*, endothelin receptor type B; *EDN3*, endothelin 3; *GDNF*, glial cell line–derived neurotrophic factor; *GFRA1*, GDNF family receptor α-1; HD, Hirschsprung disease; L-HD, long-segment HD; MEN, multiple endocrine neoplasia; *NRTN*, neurturin; RET, rearranged during transfection; S-HD, short-segment HD; SOX, SRY (sex determining region Y)-box 10.

uncharacterized *NOS1* exon 1c promoter SNP (-84G/A SNP) had an increased risk of HPS developing (odds ratio, 8.0; 95% confidence interval, 2.5 to 25.6), which could indicate that the -84G/A promoter SNP alters expression of *NOS1* exon 1c or is in linkage dysequilibrium with a functionally important sequence variant elsewhere in the *NOS1* 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 *NOS1* gene with a familial form of HPS.[47] 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.[29] In summary, genetic alterations in the *NOS1* exon 1c regulatory region influence expression of the *NOS1* 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 for 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.[48,49] 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 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 his or her 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 remains controversial; however its tremendous potential cannot be denied, and significant strides in safety have been made in the past few years. The year 2000 brought the first clinical gene therapy success—treatment of X-linked severe combined immune deficiency (XSCID)[50]—only to have this dramatic achievement undermined by the induction of leukemia by a mechanism of insertional oncogenesis in four of the nine successfully treated patients.[51] This and other adverse events[52,53] threatened to overshadow the substantial progress made in gene transfer technology in recent years. The adversity has accelerated progress in our understanding of the mechanisms of insertional oncogenesis and in the design of vectors with much lower propensity to induce malignancies.[54] Methods for gene transfer are being developed that have greater safety, specificity, and efficacy than ever before. With improved understanding of the risks and better vector design, several recent trials of gene therapy for immunodeficiency disorders[55] and for ocular disease[56] have demonstrated early success. 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).

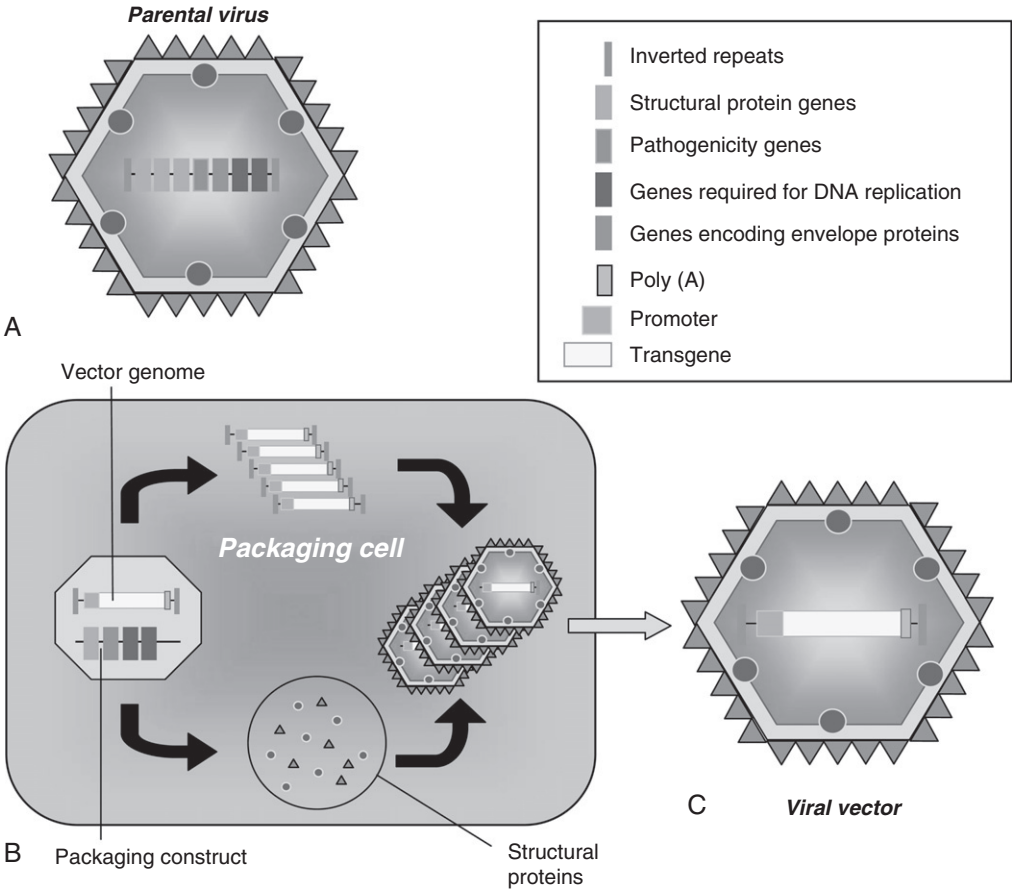


FIGURE 2-3 Requirements for the creation of a generic viral vector. **A,** The basic machinery of a chosen parental virus is used, including genes encoding specific structural protein genes, envelope proteins, and proteins required for DNA replication, but not genes encoding proteins conferring pathogenicity. **B,** The vector is assembled in a packaging cell. A packaging (helper) construct, containing genes derived from the parent 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.

TABLE 2-2
Five Main Viral Vector Groups

Vector	*Coding*	*Packaging Capacity (kb)*	*Tissue Tropism*	*Vector Genome*	*Type Advantages*	*Material Disadvantages*
Retrovirus	RNA	8	Dividing cells only	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.

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 currently 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 must 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.[57] Oncoretroviruses and lentiviruses differ in their ability to penetrate an intact nuclear membrane. Retroviruses can transduce only dividing cells, whereas lentiviruses can naturally penetrate nuclear membranes and can transduce nondividing cells, making them particularly useful for stem cell targeting applications.[58,59] Because of this difference, lentivirus vectors are superseding retrovirus vectors for most applications. Because of their ability to integrate, both types of vector share the potential hazard of alteration of the host cell genome. This could lead to the undesirable complications of human germline alteration or insertional mutagenesis, particularly important considerations for pediatric or fetal gene therapy.[2] 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.[60,61] The most important advance, however, has been the development of helper-dependent adenoviruses (HD-Ads) from which all viral genes are deleted, thus eliminating the immune response to adenoviral-associated proteins.[62] 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 AAV vector genome after transduction remains episomal, an approximately 10% rate of integration has been observed.[63] 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. This obstacle has been overcome by the development of double-strand vectors that exploit a hairpin intermediate of the AAV replication cycle.[64] 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.[65,66] 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.[67] Although most rAAV vectors have been derived from AAV2, nine 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

The adverse events described previously 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.[68] Great progress has been made in reducing T-cell responses against adenoviral antigens by the development of HD-Ad vectors from which all adenoviral genes are deleted. These vectors have demonstrated reduced immunogenicity with long-term phenotypic correction of mouse models and negligible toxicity.[69,70] However even HD-Ad vectors or less immunogenic vector systems such as AAV or lentivirus vectors can induce an immunologic response to capsid proteins[71] or to novel transgene encoded proteins,[72] 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.[73]

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. Wild-type virus infections are generally restricted to those tissues that are accessible through the route of transmission, whereas 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.[68] 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.[74] Another approach is the conjugation of capsid proteins to molecular adapters such as bispecific antibodies with specific receptor binding properties.[75,76] 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.[77] 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 in two trials of retroviral gene therapy for XSCID[50,78] leukemia developed in 5 of 20 patients treated.[51,79] 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.[80] 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.[81] 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. Even without site-specific integration, vector design, such as inclusion of a self-inactivating long terminal repeat in lentiviral vector design, can markedly reduce the likelihood of insertional mutagenesis.[54]

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.[2] 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 promising,[82] as are the successful trials for ocular disease[56] and adenosine deaminase SCID[55] mentioned previously. 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.

The complete reference list is available online at www.expertconsult.com.

CHAPTER 3

Impact of Tissue Engineering in Pediatric Surgery

Howard I. Pryor II, David M. Hoganson, and Joseph P. Vacanti

Tissue engineering is a rapidly developing interdisciplinary field at the intersection of clinical medicine, cellular biology, and engineering. The goal of tissue engineering is to create living replacement organs and tissues to provide, restore, maintain, or improve lost or congenitally absent function.[1] Early attempts by surgeons to restore function include various wooden and metal prostheses mentioned in the Talmud and a description of a rhinoplasty using a forehead flap detailed in the *Sushruta Samhita* from around 6 BC. Modern medicine has embraced both the use of manufactured substitutes (such as Dacron aortic grafts) to repair abdominal aortic aneurysms and the approach of redirecting autologous tissue for a new function, as in the transfer of a toe to replace a finger. In the past half-century, the development of immunosuppressive medication has allowed for allogeneic substitution of tissues, as in organ transplantation, demonstrating that functional replacement can be lifesaving.

Unfortunately, all these approaches have significant limitations. In pediatric surgery, prosthetic material poses several problems, including material failure, increased rates of infection, and immunodestruction of foreign material. In addition, nonliving material does not grow with the patient nor does it adapt to changing circumstances, so pediatric patients may need to undergo multiple operations with increasing levels of complexity. Native substitutions of tissue are limited by the dilemma of prioritizing the value of various tissues and accepting the functional tradeoff that must be made when redirecting tissue to new functions. The effectiveness of organ transplantation is limited by a short supply of donor organs and a long list of associated morbidities related to lifelong immunosuppression. None of these approaches has permanently solved the need to replace composite tissues.

The field of tissue engineering evolved from the collaboration of Dr. Joseph Vacanti, a pediatric surgeon, and Robert Langer, Ph.D., a chemical engineer, in the laboratory of Dr. Judah Folkman at Children's Hospital Boston as a response to the need for replacement composite tissues. In a white paper published by the National Science Foundation, it was observed that "most lead authors in Tissue Engineering have worked at least once with Langer and Vacanti."[2] Tissue engineering is considered specifically applicable to pediatric surgery because the durability of surgical therapy must be greatest in children. The outcome may be measured over decades, and the surgical reconstruction is subjected to higher levels of growth and physiologic change. This can be especially challenging for congenital defects in which the amount of available donor tissue may be insufficient and prosthetic material may not approximate the functional, cosmetic, and growth requirements of the missing tissue. Satisfying this ongoing medical need is the focus of tissue engineering.

Interdisciplinary Approach

Engineering is fundamentally different from science. The goal of science is to understand and define natural relationships. In contrast, the goal of engineering is to take advantage of relationships defined by science to address problems with solutions that do not exist in nature.[3] Engineering has been defined as the creative application of "scientific principles to design or develop structures, machines, apparatus, or processes" to solve a specific problem.[4] An engineer's invention must be communicated in concrete terms, and it must have defined geometry, dimensions, and characteristics. Engineers usually do not have all the information needed for their designs, and they are typically limited by insufficient scientific knowledge.[3] Traditionally, engineering has been based on physics, chemistry, and mathematics and their extensions into *materials science*, solid and *fluid mechanics*, thermodynamics, transfer phenomena, and systems analysis.[5] Tissue engineering is an approach that attempts to combine these traditional engineering principles with the biologic sciences to produce viable structures that replace diseased or deficient native structures.[6] As of 2004, aggregate development costs in tissue engineering exceeded $4.5 billion, and the field has encountered the kinds of challenges converting bench-top science into clinically marketable tools that were experienced during the development of other breakthrough medical technologies.[7]

Unlike biologic scientists, tissue engineers are not free to select the problems that interest them. Instead, tissue engineers must tackle the problems that present clinical

dilemmas. Frequently, the solutions must satisfy conflicting requirements; for instance, safety improvements increase complexity, but increased efficiency increases costs.[5] Problem solving is common to all engineering work. Although the problems may vary in scope and complexity, a common engineering design approach is applicable (Fig. 3-1). First, the problem is thoroughly analyzed, and a preliminary solution is selected. The preliminary solution is further subdefined by the identification of design variables that must be addressed. The preliminary solution is then refined by accounting for as many variables as possible and creatively synthesizing a new preliminary design. The preliminary design is checked for accuracy and adequacy. Finally, the results are interpreted in terms of the original problem. If the results are satisfactory, the engineering design process is complete. If the results do not adequately resolve the original problem, the design is analyzed for failure points, and the process is repeated until the original problem is solved.[5]

The short history of tissue engineering is replete with examples of this approach. For instance, monolayer cell culture has been used in the biologic sciences for decades, but this culture system typically supports only small numbers of cells in poorly organized sheets. Early attempts to organize these sheets into more clinically relevant constructs focused on the addition of an underlying support or scaffold for the cells as a substitute for the extracellular matrix (ECM).[8–11] Although these innovative approaches improved the handling characteristics and achievable cell mass of these constructs, new problems were identified in terms of poor clinical function, and the iterative process was begun anew, leading to the development of bioreactors. Early bioreactors were dynamic tissue culture devices with simple mechanical designs meant to provide oxygen exchange, defined nutrient flow rates, and electrical and mechanical stimulation that more closely approximated physiologic conditions. The results of these studies revealed further improvements in cell morphologic features, growth characteristics, and metabolic activity.[12–14] As the field of tissue engineering matures, the design variables that must be addressed for each construct will be expanded and refined accordingly.

Several fundamental biology-limited design variables of tissue engineering have been identified, including cell source, ECM, co-culture cell populations, and culture environment (Fig. 3-2). Many initial studies focused on the use of

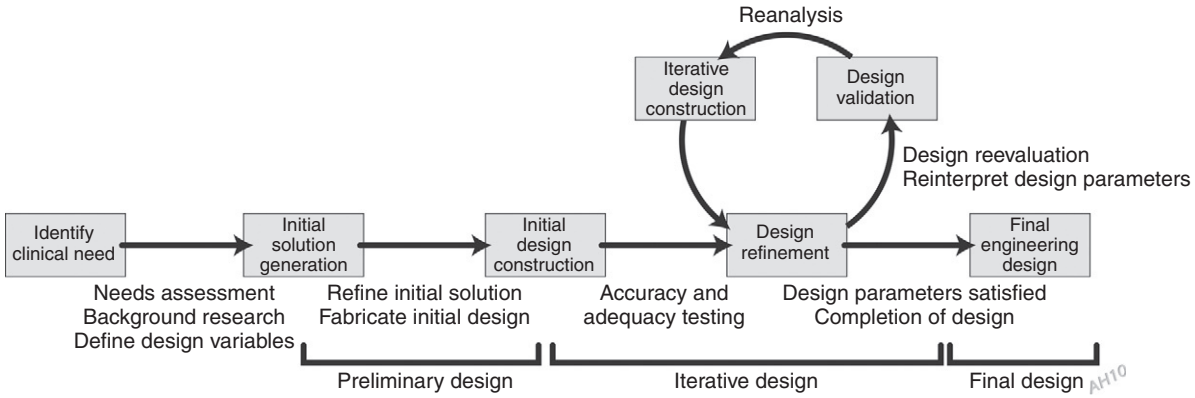


FIGURE 3-1 The iterative engineering design process. The engineering design process begins with the identification of a problem. The problem is analyzed to assess the minimum solution requirements, research the background of previous work, and define the variables that must be addressed. The preliminary design phase begins with an initial solution design and ends when the preliminary design is constructed. The iterative design phase begins with testing of the preliminary design and proceeds through design refinement, validation, and creation of subsequent designs. If a secondary design fails to satisfy initial requirements, the iterative process is undertaken repeatedly until the criteria are met. The final design phase is characterized by the formal definition of the satisfactory design through mathematic equations, drawings, and operating parameters.

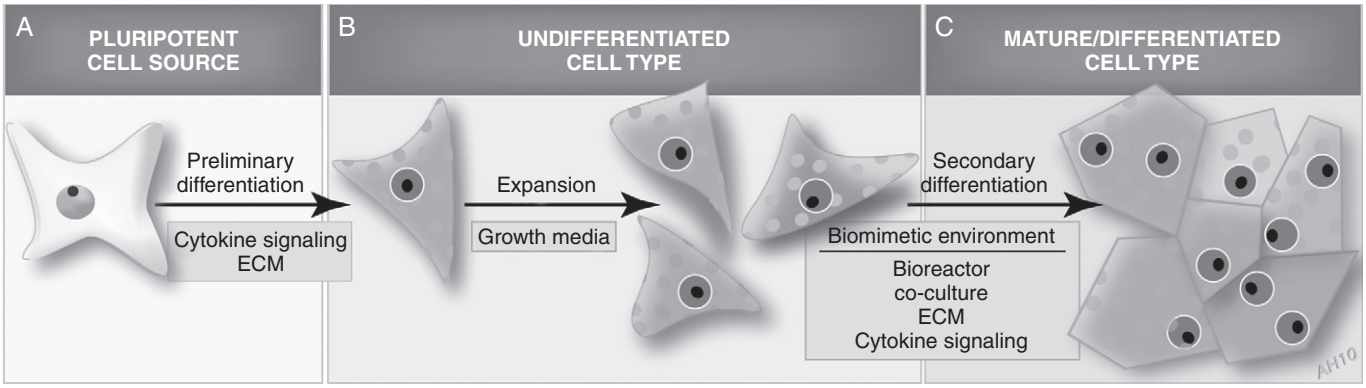


FIGURE 3-2 Multipotent cell differentiation. Pluripotent cell populations have the ability to expand in culture and differentiate into a variety of mature cell types. **A,** The process begins with expansion of the pluripotent cell type in the presence of ECM and cytokines that preserve their expandability while focusing their differentiation down the desired lineage. **B,** The partially differentiated cells are then expanded in growth media to clinically significant quantities. **C,** Using biomimetic culture techniques—including ECM, cytokine signaling, co-culture, and bioreactors—the cells are differentiated into the desired mature cell type.

autologous organ-derived, fully differentiated parenchymal, or primary, cells. Because primary cells are typically in short supply and do not naturally replicate in large quantities, several other cell sources have been investigated, including autologous bone marrow and adipose-derived mesenchymal stem cells, umbilical cord blood cells, Wharton jelly–derived cells, amniotic fluid cells, and allogeneic embryonic stem cells.[15–21] These cell populations have the ability to expand in culture and have demonstrated adequate plasticity to differentiate into a variety of cells, including the epithelium of liver, lung, and gut, as well as the cells of both hematopoietic and endothelial systems.[16,17,22–25] As the differentiation scheme for each of these cellular populations becomes clarified, it has been suggested that cell banks for tissue-engineering applications be developed to respond more rapidly to the clinical need for tissue-engineered constructs.[26]

As more immature cell populations have been investigated, the essential role of ECM in differentiation and maintenance of organ structure has become apparent. For structural tissue constructs such as bone, merely providing the cell population with a polymer scaffold with properties similar to type I collagen has proved less satisfactory than adding elements commonly found in forming bone, such as hydroxyapatite or calcium phosphate.[26–29] Similarly, in liver tissue constructs that use collagen, Matrigel and PuraMatrix hydrogel sandwiches have resulted in greater hepatocyte longevity.[30,31] Work in liver tissue engineering also demonstrated the benefit of co-culturing primary cells with tissue-specific supporting cells.[32] The adult liver requires many complex cell-cell interactions for coordinated organ function, and in vitro investigations have shown that co-cultured hepatocytes and nonparenchymal cells were more tolerant of the culture environment.[33] Co-culture of embryonic stem cells with adipose-derived mesenchymal stem cells (ADSCs) or fibroblasts resulted in enhanced culture viability and formation of vascular tubelike structures.[12,22,34] Even with the correct combinations of cells and ECM, the culture environment must mimic the in vivo environment for the tissue construct to demonstrate clinical function. A fundamental limitation of the field to date has been the adequate mass transfer of nutrients and oxygen to meet the metabolic needs of tissue constructs. The driving force for mass transfer is a concentration gradient that must be kept in perfect balance with the supply of depleted resources precisely as they are used, perpetuating the net transfer of mass from an area of high concentration to an area of low concentration.[35] In addition to a precisely tuned nutrient supply, the mechanical and anatomic in vivo environment must also be mimicked. For cardiac tissue engineering, this has been shown to be important, because constructs cultured without electrical and mechanical stimulation fail to meet critical design criteria when compared with constructs in a biomimetic environment.[6] Highly complex flow bioreactors have been designed to systematically quantify the independent and coupled effects of cyclic flexure, stretch, and flow on engineered heart valve tissue formation in vitro.[36] Researchers have evaluated tissue-engineered heart valves using a bioreactor that automatically controls mean pressure, mean flow rate, beat frequency (heart rate), stroke volume, and the shape of the driving pressure waveform.[37] In addition, researchers studying the liver have developed a biomimetic flat-plate bioreactor system housing phenotypically stabilized hepatocyte-fibroblast co-cultures in an effort to recapture the zonal features of the liver.[38]

However, the nascent field of biomimetic bioreactors has only recently begun to bring the entire weight of the field of engineering to bear. Three critical advancements that the broad field of engineering will lend to the field of tissue engineering are computational fluid dynamics, advanced modeling, and real-time culture monitoring. Computational fluid dynamics is a technique of design analysis that allows for the accurate prediction of shear stress, culture medium dynamic velocity, and mass transfer of nutrients and oxygen.[36] This technique can be applied as a modeling method in which a virtual design is created and tested by simulation. The virtual design can then be refined and retested several times before the expense of building a real prototype.[6,36,37] This modeling strategy has been applied in a few instances to predict the production of collagenous ECM in engineered tissues, to accurately reproduce scaffold mechanical properties, and to mathematically model oxygen transport in a bioreactor.[6,36,38,39] This type of modeling in the field of tissue engineering will allow for the development of theoretical frameworks to model complex biologic phenomena that can be used to guide sound, hypothesis-driven examinations of new problems and analyze engineered implant performance in vitro and after implantation.[6] The broad field of engineering will also provide the monitoring strategies required to define success in the development of tissue-engineered constructs. One example is the use of nondestructive, high-resolution, nonlinear optical microscopic imaging to observe the development of collagen in tissue-engineered constructs over time.[40] Another example of advanced monitoring is the use of a computer-controlled closed-loop feedback bioreactor to study the effects of highly controlled pulsatile pressure and flow waveforms on biologically active heart valves.[37] As the field of tissue engineering evolves, the need for thoughtfully designed, well-monitored biomimetic culture systems that emulate physiologic conditions will be required to understand the complex culture protocols necessary to yield functional tissue grafts.[14,41]

Cartilage and Bone Tissue Engineering

Pediatric surgeons encounter many congenital and acquired problems that are characterized by structural bone and cartilage defects. These defects may range from cleft palates and craniofacial abnormalities to significant long bone defects after cancer surgery. The current standard of care for most of these lesions includes bone grafting, but donor site morbidity after bone graft harvest remains a recognized limitation to this technique.[42] Grafting in children is also complicated by the fact that the pediatric skeletal system is still developing and the thickness of the nascent bone is thinner compared with adult bone.[43] To supplement the grafting approach, tissue engineers have sought to generate greater quantities of bone and cartilage. One of the earliest successes in bone and cartilage tissue engineering stemmed from the observation that chondrocytes harvested from articular surfaces differentiated in culture to cartilage, whereas chondrocytes from periosteum initially resembled cartilage but progressed in culture to

form new bone.[44] In the ensuing 15 years, the tissue engineering of bone and cartilage has evolved into a complex interaction of osteoinductive factors, osteoprogenitor cells, advanced scaffold technology, and an adequate blood supply.[25]

Cartilage is a relatively simple tissue with limited spontaneous regenerative capacity and a low metabolic rate.[45,46] However, early studies with polymer constructs of polyglycolic acid and polylactic acid molded into predetermined shapes led to the formation of cartilage in the shape of a human ear, a temporomandibular joint disk, and articular cartilage for meniscus replacement (Fig. 3-3).[47–50] Since these early studies, an entire research and industrial complex has evolved to develop adequate cartilage replacements for clinical use; a summary of the entire body of work would be beyond the scope of this book. The two principal limitations to the use of most of the resulting constructs are (1) the low replication rate of primary chondrocytes and (2) the relatively low construct strength compared with native tissue.[51] Several groups have addressed the cell source issue through the evaluation of stem cells focusing primarily on bone marrow–derived and adipose-derived mesenchymal stem cells. Both cell types are easily isolated and can be induced to secrete myriad cartilaginous ECM components after differentiation in chondrogenic culture conditions.[52,53] However, increasing construct cell density through the use of a stem cell source is not enough to address the issue of low construct strength. Several groups have shown that cartilaginous ECM secretion and subsequent construct strength are increased when constructs are cultured under dynamic conditions. Such conditions include constant media perfusion, biaxial loading, and rolling media bottle bioreactors.[41,52,54] In each case, the histologic presence of cartilage ECM was markedly increased, and the compressive force sustained by each construct was significantly increased compared with controls. However the optimum culture conditions remain undefined and will likely be unique for each cartilage type applied in the clinical setting.

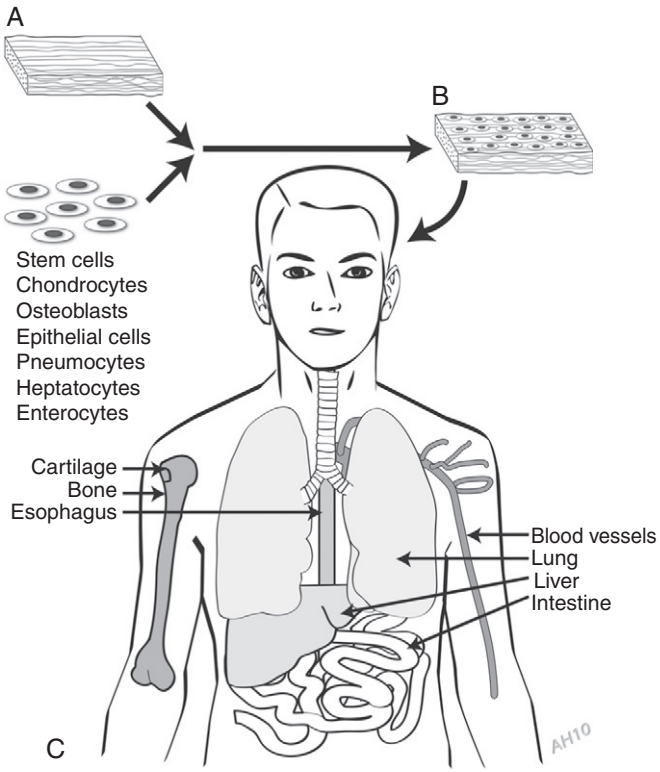


FIGURE 3-3 The classic tissue-engineering paradigm. **A,** The classic tissue-engineering paradigm is based on the expansion of pluripotent or primary parenchymal cells in static culture and the creation of a biocompatible polymer scaffold. **B,** The expanded cellular population is seeded onto the scaffold and allowed to expand further in culture. **C** The tissue-engineered construct can then be implanted in a variety of positions to replace absent or lost tissue.

The tissue engineering of bone evolved from early studies in cartilage tissue engineering in which bovine periosteal cells were seeded onto polyglycolic acid scaffolds to repair cranial bone defects in nude rats.[55] Since these first steps, bone tissue engineering has been approached in many ways. Several methods have been tried, including the implantation of collagen scaffolds containing stem cells transfected with a virus for BMP-2 (a bone forming protein), which demonstrated accelerated osteogenesis.[25,56] Cellular implantation studies have demonstrated that biomimetic scaffolds with porosity greater than 90% and a pore size ranging from 300 to 500 μm improve bone tissue regeneration.[57,58] Ultrastructural evaluation has shown that when bone scaffolds contain nanometer surface features, bone regeneration can be further optimized.[59] As a tissue, bone is significantly more vascular than cartilage, and a principal limitation to bone construct size has been the diffusion distance from surface to center of the construct. One recent approach to this problem is the technique of coculturing mesenchymal stem cells with endothelial cells in a fibronectin-collagen gel to induce spontaneous angiogenesis within the construct.[60] The use of vascular endothelial growth factor–releasing ADSCs and endothelial cells to more closely mimic the environment of developing bone and direct the growth of blood vessels into 3D PLAGA scaffolds has also been reported.[61] Applying typical engineering analytic tools, a mathematic framework for predicting the development of engineered collagenous matrix has been developed.[40] Some groups have taken advantage of the bone's natural regenerative capacity to use the periosteal space as a bioreactor to develop autologous bone grafts between the surface of a long bone and its periosteum.[13] Given the pace at which this field of tissue engineering is advancing, bone and cartilage tissue engineering will likely provide the most short-term clinically useful products, including constructs to address joint reconstruction and complex congenital anomalies with which pediatric orthopedic surgeons must contend.

CARDIAC TISSUE ENGINEERING

Approximately 1% of all newborns are diagnosed with cardiac defects, including valvular disorders, making heart malformations the most common pathologic congenital condition in humans.[26] Limited options exist for the successful treatment of these patients and include mechanical valve replacement, biologic valve replacement, and ultimately, heart transplantation. Mechanical valves are an imperfect solution because they require lifelong anticoagulation and can spawn systemic thromboembolism.[62] Biologic valves do not require systemic anticoagulation but often calcify, and they must be replaced after several years.[59] Although heart transplantation is the ultimate therapeutic option, this modality is limited by the scarcity of suitable donor organs, requires lifelong immunosuppression, and is associated with serious complications,

such as kidney failure and malignancies.[26] The perfect solution to this clinical dilemma would be the development of a nonthrombotic, self-repairing tissue valve replacement that grows with the patient and remodels in response to in vivo stimuli.[59,63]

Over the past decade, an enormous amount of research has been focused on developing a tissue-engineered heart valve meeting these criteria. Although a thorough review would be outside the scope of this book, highlights from such research illustrating tissue engineering's interdisciplinary approach follow.

Initial studies evaluated single-cell populations grown on biocompatible scaffolds in static culture conditions and clearly demonstrated short-term hemodynamic functionality with minimal calcification when implanted in sheep.[64,65] Valves co-cultured with autologous medial and endothelial cells before implantation were shown to function in vivo for up to 5 months and resemble native valves in terms of matrix formation, histologic characteristics, and biomechanics.[66] It was hypothesized that further improvement in valve performance could be obtained by culturing valves under pulsatile flow to generate a biomimetic environment resembling in vivo conditions.[6] Valves cultured under these conditions have demonstrated increased mechanical strength and improved cellular function within the construct.

Although a great deal of progress has been made in the pursuit of a tissue-engineered heart valve, these valves still need to be tested and succeed in the aortic position, where they are needed most.[63] Furthermore, the critical ability of these tissue-engineered constructs to grow with the patient must be clearly demonstrated and will be the focus of the next decade of research.

Vascular Tissue Engineering

In addition to valvular repair, children with complex *congenital heart defects* often require a new vascular conduit to reroute blood flow due to an anomaly. One such example is the Fontan procedure, in which *venous blood* is directed to the *pulmonary arteries* without passing through the *right ventricle*.[67] A host of synthetic and biologic conduits have been deployed in this location, but none of them has provided perfect results. Synthetic conduits incite a foreign body reaction and are a significant cause of thromboembolic complications.[68] Biologic grafts have significantly lower thromboembolic complication rates compared with synthetic grafts but become stenotic and calcify over time because of an immune-mediated process found to be more aggressive in younger patients.[69,70] Moreover, both graft types lack significant growth potential, and it is assumed that all such conduits will eventually need to be replaced.[69,71] Given the morbidity of repeated open-heart procedures on a child, investigators have looked to tissue engineering as an alternative to the use of synthetic and biologic conduits.[72]

As the most successful example of applied tissue engineering to date, Shin'oka and colleagues reported the first human use of a tissue-engineered blood vessel in a 4-year-old girl to replace an occluded pulmonary artery after a Fontan procedure (Fig. 3-4).[72] The conduit used was a 1:1 polycaprolactone, polylactic acid copolymer scaffold seeded with autologous peripheral venous endothelial cells. After 7 months of follow-up, no complications were noted. This successful experience has launched a clinical trial of 42 patients receiving similar scaffolds seeded with autologous bone marrow–derived cells.[73] At 16 months of follow-up, the group reported no significant complications, although one patient died from unrelated causes. The harvest of bone marrow–derived cells is associated with several morbidities, including pain and infection, so several alternative cells sources have been sought. Two such cell sources include adipose-derived endothelial progenitor cells and umbilical cord–derived cells.[23,74]

As the interdisciplinary approach of tissue engineering has been applied to the development of the tissue-engineered vascular graft (TEVG), several areas for improvement have been identified. Using a bioreactor that provided physiologic stimulation similar to the pulmonary artery, physiologically

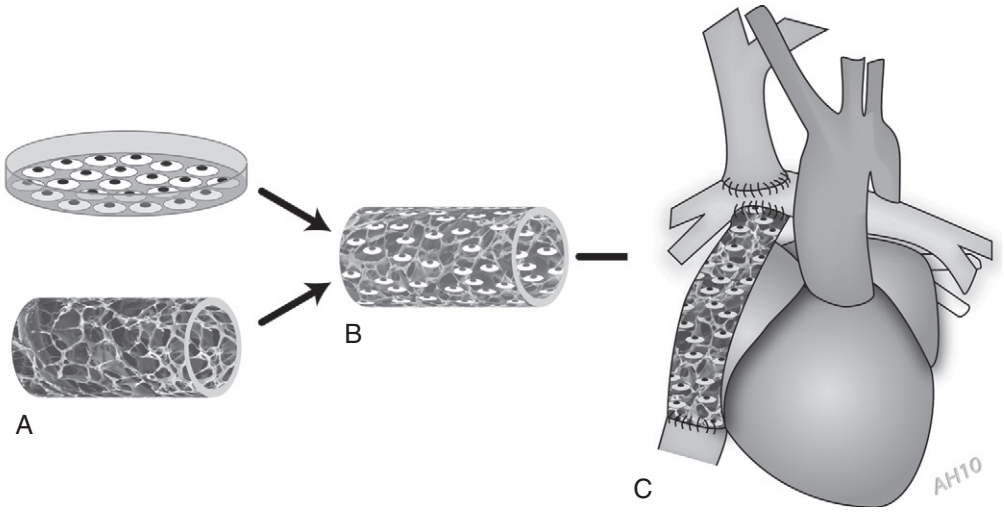


FIGURE 3-4 Tissue-engineered vascular graft. **A,** Tissue-engineered vascular grafts are constructed from a host of cells expanded in culture (autologous peripheral venous endothelial cells, bone marrow–derived cells, adipose-derived endothelial progenitor cells, and umbilical cord–derived cells) and a conduit composed of 1:1 polycaprolactone and polylactic acid copolymer scaffold. **B,** The expanded cellular population is seeded onto the construct and allowed to attach in culture before implantation. **C,** The tissue-engineered vascular graft has been used as an extracardiac conduit in the Fontan procedure.

dynamic conditions up-regulated collagen production by fourfold over the static controls in an in vitro TEVG.[37] Sophisticated monitoring techniques have been developed to evaluate TEVG for the development of normal vascular architecture. Qualitative immunohistochemical and quantitative biochemical analyses demonstrate that the ECM of the TEVG resembled the ECM of the native inferior vena cava after explantation in animal studies.[75]

This type of successful translation of cardiovascular tissue-engineering principles from the bench to the clinic could lead to improved vascular grafts for other cardiovascular surgical applications.[68] Two obvious applications of this developing field are small-diameter vascular grafts and new vascular stent materials.[59] The development of a small-diameter tissue-engineered graft could fill a significant void in the field of vascular surgery, because grafts smaller than 6 mm cannot be satisfactorily constructed from textile or polytetrafluoroethylene (PTFE) and must be bypassed with autologous arteries and veins, with a limited supply for multiple operations.[76] Further, the development of an inexhaustible supply of vascular constructs for in vitro use could lead to the rapid advancement of stenting technologies by eliminating the expense and time expended in animal trials. The pursuit of these near-term goals would result in a dramatic expansion of the field of tissue engineering over the next 10 years.

Gastrointestinal Tissue Engineering

Gastrointestinal tissue engineering has the potential to improve outcomes in two clinical settings for pediatric surgeons: esophageal atresia and short-bowel syndrome. Long-gap esophageal atresia is a daunting clinical problem requiring delayed repair and transposition of a remote portion of bowel.[77–79] Complications from these procedures abound, including stricture, leakage, and malnutrition secondary to shortening of the gastrointestinal tract.[80,81] Moreover, synthetic conduits are unavailable and would lack the critical ability to grow with the patient throughout childhood. As a result, many groups have sought to develop a tissue-engineered esophageal construct that could be used to treat long-gap atresia. Initially, it was demonstrated that organoid units transplanted from adult autologous esophagus onto a biodegradable scaffold form complex tissue indistinguishable from native esophagus.[82] Tissue-engineered esophagus has been used both as a patch and as an interposition graft in rats in preliminary studies.[82] However, these organoid units required resection of significant esophageal length. Recent studies have revealed that isolated esophageal cells could be seeded under low density on collagen polymers and could be expanded in vitro, leading to a potential autologous tissue–engineered esophageal construct.[83]

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.[84,85] This clinical condition develops when less than one third of normal jejunal-ileal length remains, a distance of 25 to 100 cm in neonates.[86] Pediatric surgeons influence the morbidity and mortality of patients with pediatric gastrointestinal disorders such as inflammatory bowel disease and necrotizing enterocolitis because these disorders can require resection of large portions of small bowel.[20,87] Despite efforts to maximize bowel preservation at the time of surgery and the use of gut lengthening procedures to extend the remaining small bowel's functional surface area, many patients become dependent on total parenteral nutrition.[88] These patients are at risk for liver dysfunction as a result of impaired enterohepatic bile salt circulation and abnormal bile acid metabolism, resulting in overt liver failure. This liver dysfunction is recognized as an indication for small intestine transplantation, a procedure fraught with poor survival and lifelong morbidities.[89]

The generation of a composite tissue resembling small intestine from intestinal cells heterotopically transplanted as organoid units was first reported in 1998.[86] Organoid units were derived from full-thickness harvests of intestine and loaded on 2-mm cylindric bioresorbable polymers before implantation in the omentum. The resulting engineered bowel demonstrated polarization of the epithelial cells, which faced the lumen of the cyst. The other layers of the intestinal wall were histologically present with substantial vascularization.[86] Subsequent studies have evaluated a variety of scaffold and cellular combinations that further improve the clinical potential of this therapy.

These evaluations revealed that the ability of intestinal organoid units to recapitulate full-thickness bowel was based on the presence of a mesenchymal core surrounded by a polarized intestinal epithelium, representing all the cells within a full-thickness section of bowel.[90,91] The neomucosa generated by this method in rats demonstrated epithelial barrier function and active transepithelial electrolyte movement equal to that of native adult tissue.[86] Additional studies have supported the finding that the neointestine is not merely anatomically intact but is able to absorb energy-dense nutrients, suggesting a future human application for tissue-engineered intestine.[20] Unfortunately, the use of organoid units requires invasive procedures for harvest, and a more ideal cell source is needed. Such a source would possess the ability to differentiate into all aspects of the intestine, including absorptive and secretory cells as well as vasculature and physical support structures.[20]

The ideal scaffold material has similarly not yet been identified. Initial work on the topic evaluated several options, including AlloDerm and small intestinal submucosa (SIS).[92,93] The latter has been used to support mucosal regeneration across a gap in resected bowel in experimental models.[94] It has also been shown to degrade within 3 months after operative implantation replaced by host-derived tissue.[95] In one large animal study, a commonly used human biomaterial, polyglycolic acid, was used as the scaffold for the first engineered intestine implanted during a single anesthetic administration. It was seeded with autologous tissue arising from organ-specific stem cells.[96] Although all these results point to a future tissue-engineered construct that increases absorptive surface area, a future challenge will focus on the recovery of peristaltic activity of the regenerated bowel. This will require advances in both smooth muscle incorporation and reinnervation of the regenerated bowel.[95] Tissue-engineered gastrointestinal replacement with peristalsis would provide a critical advancement in the treatment of many pediatric surgical diseases and may significantly affect patient care, with improved surface area, transporter function, immune characteristics, and architecture.

Liver Replacement and Tissue Engineering

The liver is a complex vital organ that supports homeostasis through metabolism, excretion, detoxification, storage, and phagocytosis of nutrients and toxins. Acute or chronic liver dysfunction accounts for the death of 29,000 Americans each year, with acute failure mortality rates exceeding 80%.[97,98] In children, liver dysfunction can be caused by biliary atresia–related liver cirrhosis and metabolic diseases such as alpha-1 antitrypsin deficiency, Wilson disease, tyrosinemia, and others.[99] Despite investigation into a wide array of liver support protocols, orthotopic liver transplantation remains the only definitive treatment for severe hepatic failure. Three thousand of these procedures are performed annually, leaving thousands of patients on waiting lists in need of an alternative option. The field of hepatic tissue engineering developed as an attempt to solve this problem.

Initial studies in the field of hepatic tissue engineering were based on the injection of isolated hepatocytes into the portal vein, peritoneal cavity, spleen, and pancreas.[100–102] These cells engrafted and corrected both isolated and global metabolic deficiencies, but these successes were time-limited because the mass of the injected cells was small, and the functional capacity of the cells decreased over time. Methods to increase the tissue-engineered liver mass included concurrent hepatotropic stimulation through partial hepatectomy, portacaval shunting, and injection of liver toxins.[103–106] Even with maximal hepatotropic stimulation, these methods failed to yield adequate hepatocellular function to detoxify a patient in fulminant hepatic failure. A more advanced tissue-engineered liver construct was sought to provide temporary liver function replacement based on the concept of kidney dialysis therapy and was referred to as an extracorporeal bioartificial liver device (BAL).[107] The goal of such a device is to support patients in acute liver failure while liver regeneration occurs and, if that fails, to serve as a bridge to transplantation.[108] Unfortunately, despite a wide array of devices tested, none has delivered the desired results.[107] Most BALs tested to date contain a singular hepatocyte cell population without associated nonparenchymal cells. Such a device's lifetime is limited because hepatocytes degenerate within hours to days in such an environment.

The cellular physiology of the liver is complex. Hepatocytes are anchorage-dependent cells and require an insoluble ECM for survival and proliferation.[85] The adult liver also requires a complex cell-cell interplay between hepatocytes and the nonparenchymal cell populations, including biliary epithelium, Kupffer cells, stellate cells, and sinusoidal endothelial cells. These interactions are essential for proper organ function, and hepatocytes dedifferentiate within 2 weeks when these communications are severed.[109] To preserve and encourage these necessary interactions in future BALs, several groups have proposed to organize the underlying scaffold to serve as a template to guide cell organization and growth.[85] Given the high metabolic requirements of liver tissue, this organized structure would allow more efficient diffusion of oxygen and nutrients and removal of waste. A further advance of this concept, being refined at the Massachusetts General Hospital Tissue Engineering and Organ Fabrication Laboratory, is the development of a polymer device with an integrated vascular network to provide immediate access to the blood supply after implantation (see the discussion on future directions in the next section).[18] This de novo vascular system could be used as a template for any complex tissue such as liver or lung. Future designs are based on a modular concept that allows for the fabrication of implantable devices containing a large mass of cells within a structured environment, complete with de novo blood supply.

One significant challenge that remains entirely unaddressed in the field of hepatic tissue engineering is the development of an artificial biliary system. One solution may lie in the use of multipotent cells that can differentiate down both the hepatocytic and biliary lineages during postimplantation remodeling.[99]

Future Directions: Vascular Networks

The advances of tissue engineering have occurred primarily through interdisciplinary efforts of electrical, chemical, and mechanical engineers; scientists, in fields such as developmental biology, biomaterials science, and stem cell biology; and clinicians from surgical and medical fields.[110] This approach has been successful in the initial development of avascular or thin tissues with low metabolic activity and functions limited to mechanical activity, such as skin, bone, cartilage, and heart valves (Table 3-1).[12,18,59] Engineering more complex tissues with a significant homeostatic contribution and high metabolic activity necessitates the development of a vasculature within the construct that promotes cell survival, tissue organization, and rapid nutrient supply immediately after implantation.[12,18]

Native tissues are supplied by capillaries that are spaced a maximum of 200 μm from one another, permitting a natural diffusion limit for nutrients and gases.[111,112] Two approaches have been investigated to address this goal of providing nutrients to every cell in a tissue construct within the tissue's natural diffusion limit (Fig. 3-5).[12,113] One strategy relies on the tissue construct's natural ability to sprout new or bridging vessels or to invite ingrowth of existing vessels.[12] Despite numerous attempts, it has been difficult to develop a de novo angiogenesis-based vasculature within a tissue construct because of the challenges involved in the differentiation and sustenance of multiple (i.e., vascular progenitor and parenchymal) cell types in a concomitant fashion.[13] To date, only one group has had success in a tissue-engineered bone construct.[60] Several previous attempts to invite ingrowth after implantation have revealed that blood vessel invasion from the host tissue is limited to a depth of several hundred micrometers from the surface of the implant.[61] This results in a central zone of necrosis because only the periphery of the graft is efficiently vascularized.[60,114] The difficulties with in vitro vascularization have led to the development of an alternative solution: preformed vascular networks.[26]

The design of preformed vascular networks is only beginning to be defined as a natural extension of previously identified axioms of vascular biology. Such networks will have to be designed individually for the intended tissue based on the tissue's inherent resistance to flow, nutrient transfer requirements, and waste removal needs.[113] Such control of the microenvironmental niche within each tissue will be

TABLE 3-1
Existing Tissue Engineered Products

Brand Name	*Application*	*Manufacturer*	*Cells*	*Matrix*
Bioseed Oral Bone	Bone	BioTissue Technologies	Autologous osteocytes	Fibrin gel
Osteotransplant	Bone	Co.Don AG	Autologous osteocytes	Fibrin gel
Carticel	Cartilage	Genzyme Biosurgery	Autologous chondrocytes	
Hyalograft C	Cartilage	Fidia Advanced Biopolymers	Autologous chondrocytes	Hyaluronic acid
MACI	Cartilage	Verigen AG	Autologous chondrocytes	Collagen
Chondrotransplant	Cartilage	Co.Don AG	Autologous chondrocytes	
Bioseed-C	Cartilage	BioTissue Technologies	Autologous chondrocytes	3D fibrin matrix
NOVOCART	Cartilage	TETEC AG	Autologous chondrocytes	
Chondrotec	Cartilage	CellTec GmbH	Autologous chondrocytes	Fibrin gel
Cartilink-1 Cartilink-2	Cartilage	Interface Biotech A/S	Autologous chondrocytes Autologous chondrocytes	Periosteum Bovine collagen
Bioseed-M	Oral mucosa	BioTissue Technologies	Oral mucosal cells	Fibrin gel
Integra	Skin	Integra LifeSciences	Dermal fibroblasts	Bovine collagen
Dermagraft	Skin	Advanced Tissue Sciences, Inc.	Neonatal fibroblast	Polyglactin mesh
Apligraf	Skin	Organogenesis Inc.	Allogenic fibroblasts and epidermal cells	Bovine collagen
Epicel	Skin	Genzyme Biosurgery	Autologous keratinocytes	
Transcyte	Skin	Smith & Nephew	Human fibroblast	Polymer membrane
Hyalograft 3D Laserskin	Skin	Fidia Advanced Biomaterials	Autologous fibroblasts Autologous keratinocytes	Hyaluronic acid Hyaluronic acid
Bioseed-S Melanoseed	Skin	BioTissue Technologies	Keratinocytes Melanocytes	Gel-like fibrin Gel-like fibrin
Autoderm Cryoceal	Skin	XCELLentis	Human Keratinocytes	None
Epibase	Skin	Laboratoire Genevrier	Autologous keratinocytes	Collagen
Orcell	Skin	Ortec Inc.	Allogeneic fibroblasts Allogenic keratinocytes	Collagen
Vivoderm	Skin	ER Squibb & Sons Inc	Autologous keratinocytes	Hyaluronic acid
Acudress	Skin	Iso Tis SA	Keratinocyte precursors	Fibrin
Vascugel	Vascular	Pervasis	Allogenic endothelial cells	Gelatin sponge

Data from references 115–119.

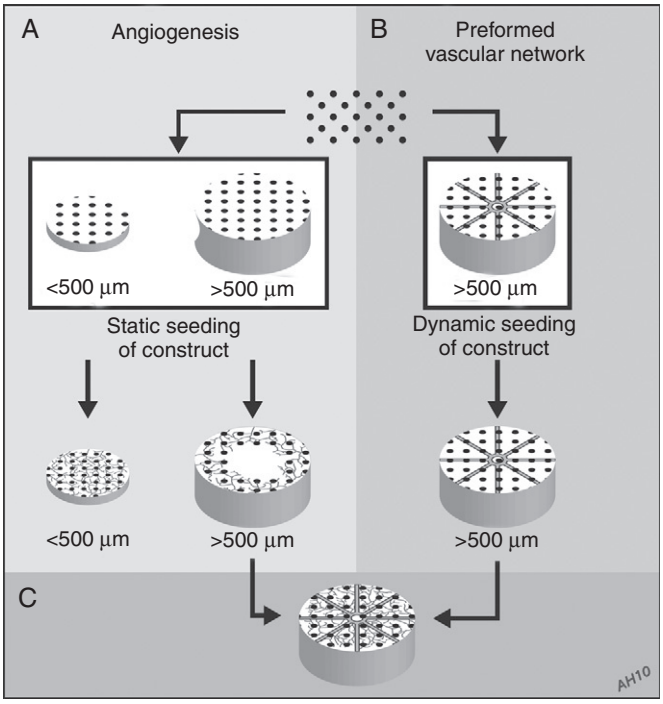


FIGURE 3-5 Angiogenesis versus preformed vascular networks. **A,** The angiogenesis approach to vascularized tissue constructs relies on the natural ability of a construct to form new vessels or invite ingrowth of existing vessels. For constructs less than 500 μm in every dimension, cells can survive on diffusion alone as new vessel ingrowth reaches the entire cellular population. For constructs larger than 500 μm, a necrotic core develops because cells greater than 500 μm from nutrients cannot survive on diffusion long enough to allow vessel ingrowth. **B,** Using tissue-specific design criteria, preformed vascular networks can provide nutrients to within 150 μm of each cell in a construct with dimensions greater than 500 μm, thereby preventing a necrotic core. **C,** Using a resorbable scaffold to manufacture the preformed vascular network will allow the network to serve as a starting point for angiogenesis in the construct while providing the required nutrients during the ingrowth process.

key to successful tissue regeneration and has only been possible because of recent manufacturing advancements in the field of mechanical engineering, such as electrical discharge machining and micromilling.[113] Such networks can serve as the "vascular scaffold" for subsequent post-implantation remodeling.[12] As solutions to these near-term limitations evolve, more problems will be identified that will require an interdisciplinary approach to tissue engineering.

The future of tissue engineering is dependent on a robust blend of fundamental iterative engineering design, developmental and cellular biology, and surgical expertise to optimize the clinical use of new engineered constructs. The initial efforts to develop clinically useful tissues have succeeded in thin tissues supplied by diffusion. Future successful efforts in the design of vascularized structures and the evolution of autologous cell sources for tissues will eventually result in the development of clinically useful tissue-engineered organs.

The complete reference list is available online at www.expertconsult.com.

CHAPTER 4

Advanced and Emerging Surgical Technologies and the Process of Innovation

Sanjeev Dutta, 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 defines either success or failure.

The development and use of tools and technologies remains a distinguishing characteristic of mankind. 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 has defined both our craft and our care since the first bone needles were used in prehistoric times.

This chapter attempts to highlight those advanced and emerging surgical technologies that shape the present and direct future changes. A framework to facilitate both thought and action about those innovations to come is presented. Finally, the surgeon's role in the ethical process of innovation is discussed. The authors remain acutely attuned to Yogi Berra's admonition, "Predictions are difficult, especially about the future."

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 of and even dependence on tools and technologies. Clamps, catheters, retractors, energy sources, and monitors fill these spaces; they facilitate and enhance surgeons' capabilities in the process of diagnosis, imaging, physiologic care, molecular triage, and in the performance of surgical procedures. Surgeons constantly function as users of technology; thus a fundamental understanding underpins their thoughtful use. The use of a drug without understanding the mechanism and side effects would be regarded as malpractice. A similar case must be made for 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. The face of a patient with the 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. Tom Fogarty's development of the balloon catheter began as a surgical assistant 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. John Gibbon's successful construction of a heart-lung machine was initially motivated by the patient with the 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, an extraordinary pediatric surgeon, innovator, and one of the most literate surgeons of the twentieth century, described surgery as an intellectual discipline characterized not only by operative procedures but also by the attitude or responsibility toward care of the sick. Dr. Ravitch's contribution to the development of stapling devices deserves enormous credit.[1]

A surgical operation can be defined as "an act performed with instruments or by the hands of a surgeon." This implies an image and a manipulation; the manipulation implies an energy source. Historically, we have regarded the "image" to be that of a direct visual image and "manipulation" performed with the direct contact of two hands or surgical tools.

TABLE 4-1
Surgical Operation: Image and Manipulation

Image	*Manipulation*
Direct visual	Two hands direct
Video image	Two hands, long tools robots
Ultrasonography (US)	Cold, thermal
Computed tomography	Radiofrequency
Magnetic resonance imaging	Photodynamic energy Focused US energy

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

Current and Future Diagnostic Technologies

Accurate evaluation of surgical disease has always been a vital aspect of surgical practice, always preceding operation. Whether in the clinic, the emergency room, or a hospital bed, precise assessment to correctly guide operative or nonoperative therapy 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 added considerably to the evaluation of surgical patients. Driven by advancements in medicine, engineering, and biology, these studies use increasingly sophisticated technologies. These technologies promise to arm surgeons with more detailed anatomic, functional, and even molecular information in the coming years.

During the last 3 decades, the introduction and improvement of US, CT, and MRI techniques have revolutionized the clinical evaluation of surgical disease. The fine anatomic data that these imaging modalities provide has facilitated the accurate diagnosis of a wide variety of conditions. Functional imaging techniques, such as positron emission tomography (PET) and functional MRI, 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 and characterization of disease, for preoperative surgical planning, and for postoperative follow-up and evaluation. This section will provide an overview of the imaging modalities used in pediatric surgery, focusing on emerging techniques and systems.

ULTRASONOGRAPHY

Ultrasound imaging has become a truly invaluable tool in the evaluation of the pediatric surgical patient. Providing anatomic as well as real-time functional information, US imaging has several unique advantages that have made it particularly useful in the care of children. These include their relatively low cost, their portability and flexibility (seamless movement from the operating room, intensive care unit, or emergency room), and their safety in children and fetuses because they do not rely on ionizing radiation. For these reasons, this section will pay particular attention to US imaging, highlighting emerging advances in its technology and practice including three-dimensional (3D) US imaging, US contrast imaging, and US harmonic imaging.

Ultrasonography uses the emission and reflection of sound waves to construct images of body structures. In essence, medical US operates on the same principle as active sound navigation and ranging (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.[2] In the body, the sound waves are primarily reflected at tissue interfaces, with the strength of the returning echoes mainly correlating with the properties of the tissues being examined. The advantages of US imaging include lack of ionizing radiation, real-time imaging with motion, and relatively fast procedure times.[3]

In modern US imagers, numerous transducer elements are placed side by side in the transducer probe. The majority of US imaging devices currently use linear or sector scan transducers. These consist of 64 to 256 piezoelectric elements arranged in a single row. With this arrangement, the transducer can interrogate a single slice of tissue whose thickness is correlated to the thickness of the transducer elements.[2] This information is then used to construct real-time, dynamic, two-dimensional images. Color, power, and pulsed wave Doppler imaging are variations of this technology that allow color or graphical visualization of motion.[3] Specifically, conventional Doppler imaging provides information of flow velocity and direction of flow by tracking scattering objects in a region of interest.[4] In contrast, power Doppler displays the power of the Doppler signal and has proven to be a more sensitive method in terms of signal-to-noise ratio and low flow detectability.[5]

In pediatric surgery, US imaging is widely used in the evaluation of multiple pathologies, including appendicitis, testicular torsion, intussusception, and hypertrophic pyloric stenosis.[6,7] In addition, US is a powerful and relatively safe tool for the prenatal diagnosis of congenital diseases. Prenatal US evaluation is useful in facilitating the prenatal diagnosis of abdominal wall defects, congenital diaphragmatic hernias, sacrococcygeal teratomas, cystic adenomatoid malformation, pulmonary sequestration, neural tube defects, obstructive uropathy, facial clefting, and twin-twin syndromes.[8] Furthermore, sonographic guidance is vital to accomplishing more invasive prenatal diagnostic techniques such as amniocentesis and fetal blood sampling.[8]

Three-Dimensional Ultrasonography

Although two-dimensional (2D) US systems have improved dramatically over the last 30 years, the two-dimensional images produced by these systems continue to require a relatively large amount of experience to effectively interpret. This stems from the fact that the images represent one cross section, or slice, of the target anatomy, requiring users to reconstruct the three-dimensional picture in their mind. Given these limitations, 3D US systems, which 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 3D US system occurred in 1986 when Kazunori Baba at the Institute of Medical Electronics, University of Tokyo, Japan, succeeded in obtaining 3D fetal images by processing 2D images on a mini-computer.[9] Since then, multiple 3D US systems have been developed with the purpose of providing more detailed and user-friendly anatomic information. These multislice, or volumetric, images are generally acquired by one of the following techniques:

1. Use of a two-dimensional array where a transducer with multiple element rows is used to capture multiple slices at once and render a volume from real 3D data.
2. Use of a one-dimensional phased array to acquire several 2D slices over time. The resultant images are then fused by the US computer's reconstruction algorithm.

The three-dimensional information acquired by these techniques is then used to reconstruct and display a 3D image by either maximum signal intensity processing, volume rendering, or surface rendering. Currently, 3D US systems are available from several manufacturers, including General Electric, Phillips, and Siemens. When these three-dimensional images are displayed in a real-time fashion; they have the ability to provide functional information on the physiology of a patient. An example of this is the evaluation of cardiac function using real-time US. Real-time, 3D US is sometimes referred to as 4D US, though it is still essentially providing a three-dimensional image. Figure 4-1 represents a 3D US view of a fetus in utero.

In the field of pediatric surgery, 3D US systems have not yet seen routine clinical application. However, their utility in perinatal medicine has been increasingly investigated. Specifically, 3D US systems have been used for detailed prenatal evaluation of congenital anomalies. In a study published in 2000, Dyson and colleagues[10] prospectively scanned 63 patients with 103 anomalies with both 2D and 3D US techniques. Each anomaly was reviewed to determine whether 3D US data were either advantageous, equivalent, or disadvantageous compared with 2D US images. They found that the 3D US images provided additional information in 51% of the anomalies, provided equivalent information in 45% of the anomalies, and were disadvantageous in 4% of the anomalies. Specifically, they found that 3D US techniques were most helpful in evaluating fetuses with facial anomalies, hand and foot abnormalities, and axial spine and neural tube defects. 3D ultrasonography offered diagnostic advantages in about one half of the selected cases studied and affected patient management in 5% of cases. They concluded that 3D US was therefore a powerful adjunctive tool to 2D US in the prenatal evaluation of congenital anomalies.[10]

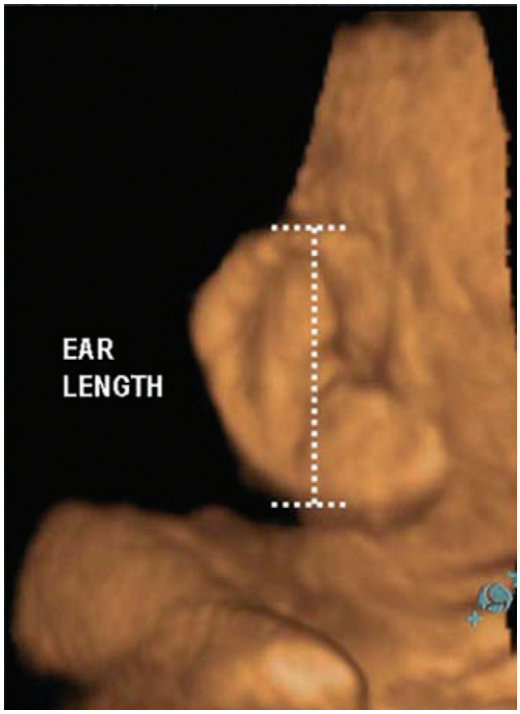


FIGURE 4-1 Three-dimensional ultrasound image of a fetal ear. (From Kurjak A, Miskovic B, Andonotopo W, et al: How useful is 3D and 4D US in perinatal medicine? J Perinat Med, 2007;35:10-27.) *(See Expert Consult site for color version.)*

Similarly, Chang and colleagues reported several series where 3D US techniques were used to effectively evaluate fetal organ volumes, estimating fetal lung volume for the evaluation of pulmonary hypoplasia,[11] cerebellar volume,[13,14] heart volume,[15] adrenal gland volume,[16] and liver volume.[17] In all of these studies, 3D US images provided more accurate data than 2D images.[11]

In 2007, Kurjak and colleagues reviewed, in *Perinatology,* the published experience with 3D and 4D US.[18] Their analysis highlighted reports detailing the use of 3D US to more accurately evaluate fetal craniofacial anomalies. In one study, 4D US was used to measure external ear length, a parameter that is classically difficult to accurately determine using 2D US. Short external ear length is one of the most consistent anthropomorphic characteristics found in neonates with Down syndrome (see Fig. 4-1). In another report, 3D US evaluation of the fetal central nervous system was found to improve the diagnosis of malformations with a sensitivity of up to 80%. More relevant to pediatric surgery, 3D US systems combined with the use of high-frequency transvaginal US probes enhanced the detection rate of cystic hygromas, with earlier and more frequent detection of these lesions. The use of 3D US to evaluate the fetal heart has also shown promise. A recently introduced US technique, tomographic US imaging (TUI), allows the examiner to review multiple parallel images of the beating heart. Using the known advantages of multislice imaging commonly used in computed tomography and magnetic resonance imaging, TUI can provide a more precise determination of the relationships between adjacent cardiac structures.

In addition to prenatal evaluation, 3D US systems have been used to image the ventricular system in neonates and infants to aid in the preoperative planning of neuroendoscopic interventions.[19,20] Similarly, these systems have seen relatively extensive use in the area of transthoracic echocardiographic imaging for the evaluation of congenital cardiac anomalies.[21,22] From an experimental standpoint, Cannon and colleagues studied the ability of 3D US to guide basic surgical tasks in a simulated endoscopic environment.[23] They found that 3D US imaging guided these tasks more efficiently and more accurately than 2D US imaging.[23] Overall, 3D US systems appear to allow the visualization of complex structures in a more intuitive manner compared with 2D systems. In addition, they appear to enable more precise measurements of volume and the relative orientation of structures.[24] 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 3D US, significant advances have recently been made with respect to US contrast imaging and harmonic imaging, which may serve to improve the quality of information obtained by US techniques and may expand the clinical use of US as an imaging modality.

Ultrasound contrast imaging techniques are currently used for the visualization of intracardiac blood flow to evaluate structural anomalies of the heart.[25] In general, US contrast agents are classified as free gas bubbles or encapsulated gas bubbles. Simply stated, these gas bubbles exhibit a unique resonance phenomenon when isonified by an US wave, resulting in a frequency-dependent volume pulsation that makes the resonating bubble behave as a source of sound, not just a reflector of it.[4] Currently, 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.[4] As these methods improve, US contrast imaging may serve to provide clinicians with more detailed perfusion imaging of the heart as well as tumors and other anatomic structures. Figure 4-2 depicts an US image of the left ventricle using microbubble contrast.

Interest in US harmonic imaging occurred in 1996 after Burns observed harmonics generated by US contrast agents.[26] Since then, significant developments have occurred in the use of the harmonic properties of sound waves to improve the quality of US images. In brief, 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. When US contrast agents are used, harmonics are generated by reflections from the injected agent and not by reflections from tissue. When no contrast is used, harmonics are generated by the tissue itself.[27]

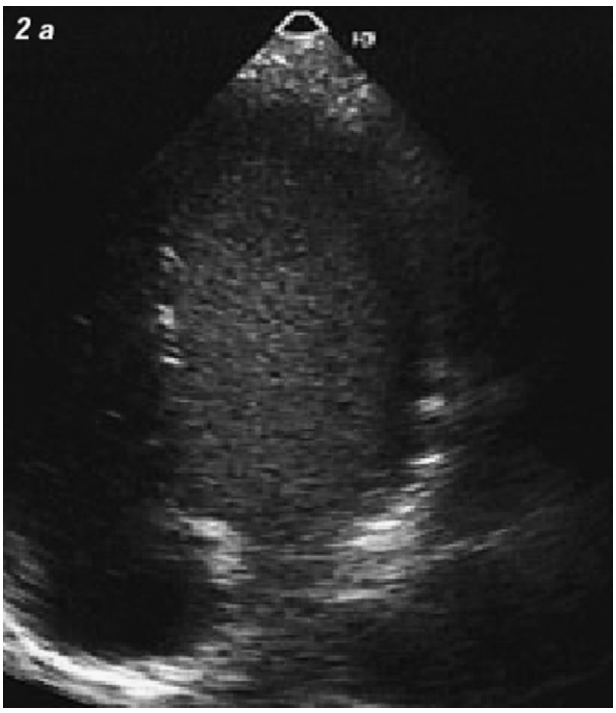


FIGURE 4-2 Ultrasound contrast image of the left ventricle. (From Frinking PJ, Bouakaz A, Kirkhorn J, et al: US contrast imaging: Current and new potential methods. US Med Biol 2000;26:965-975.)

Although 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 until natural tissue attenuation overcomes this effect. In contrast, the intensity of the fundamental frequency is attenuated linearly with depth.[27] Tissue harmonic imaging takes advantage of these properties by using the harmonic signals that are generated by tissue and by filtering out the fundamental echo signals that are generated by the transmitted acoustic energy.[28] This 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.[27] Figure 4-3 compares an image obtained by US harmonic imaging and one obtained by standard 2D US.

Ultrasonography and Fetal Surgery

With the advent of fetal surgery in 1980, US evaluation became an increasingly important noninvasive modality for diagnosing and characterizing diseases that are amenable to fetal surgical intervention.[29] 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 balloon occlusion for severe left congenital diaphragmatic hernia.[30,31] In all of these procedures, sonography currently remains the modality of choice for fetal diagnosis and treatment because of its safety and real-time capabilities. Specifically, fetal US can be used to characterize the severity of the congenital anomaly and to determine its appropriateness for intervention. During open hysterotomy, US is used to determine an appropriate location for the uterine incision away from the placenta and to monitor fetal heart rate and contractility. During procedures that do not use open hysterotomy, such as radiofrequency ablation for twin-reversed arterial perfusion sequence, laser ablation for twin-twin transfusion syndrome, and shunt placements for large pleural effusions, and bladder outlet obstruction, fetal US is used to directly guide the intervention. In addition, US imaging is vital to the postoperative care and follow-up of fetal surgical patients, because they remain in utero after their surgical procedure.

COMPUTED TOMOGRAPHY

Computed tomography was invented in 1972 by British engineer Godfrey Hounsfield of EMI Laboratories, England, and independently by South African–born physicist Allan Cormack of Tufts University, Massachusetts. Since then, the use of CT imaging has become widespread in multiple fields of medicine and surgery. Currently, advances in technology have improved the speed, comfort, and image quality of modern CT scanners. In addition, recent advances, such as multidetector CT computed tomography (MDCT) and volumetric reconstruction, or 3D CT, may be particularly valuable in

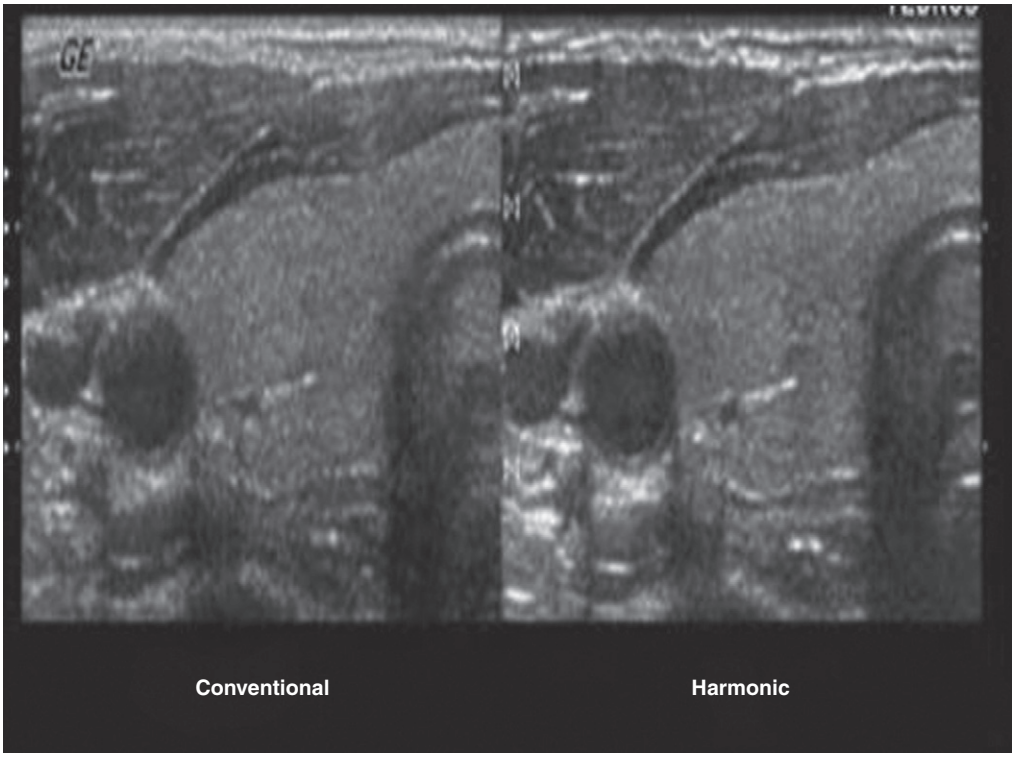


FIGURE 4-3 Conventional versus ultrasound harmonic imaging. (From Tranquart F, Grener N, Eder V, Pourcelot L, et al: Clinical use of US tissue harmonic imaging. US Med Biol 1999;25:889-894.)

the care of pediatric surgical patients. This section will provide a brief overview of CT imaging, focusing on MDCT and volumetric imaging and their implications in pediatric surgery.

Multidetector Computed Tomography

Computed tomography uses a tightly arranged strip of radiation emitters and detectors that circles around a patient to obtain a two-dimensional map of x-ray attenuation values. Numerical regression techniques are then used to turn this list of attenuation values into a two-dimensional 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.[32] Before this development, the table and patient were moved in a stepwise fashion after the acquisition of each image slice, resulting in relatively long scanning times. Helical CT scanners use slip ring technology that allows the tube and detector to continually rotate around the patient. Combined with continuous table motion through the rotating gantry, this significantly improves the speed of CT studies. The improved speed of helical CT scanners enables the acquisition of large volumes of data in a single breath hold.

Helical CT has improved during the past 15 years, with faster gantry rotation, more powerful x-ray tubes, and improved interpolation algorithms.[33] However, the greatest advance has been the recent introduction of multidetector-row CT (MDCT) scanners.[32] 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 for the clinical application of CT imaging, especially in the pediatric patient where the issues of radiation exposure and patient cooperation are magnified. Fundamental advantages of MDCT compared with earlier modalities include substantially shorter acquisition times, retrospective creation of thinner or thicker sections from the same raw data, and improved 3D rendering with diminished helical artifacts.[33]

In the pediatric population, MDCT provides a number of advantages compared with standard helical CT. Because of the increased speed of MDCT, there may be a decreased need for sedation in some pediatric studies. There is also a reduction in patient movement artifact as well as a potential for more optimal contrast enhancement over a greater portion of the anatomy of interest. The volumetric data acquired also provides for the ability of multiplanar reconstruction, which can be an important problem-solving tool. MDCT has been increasingly used for pediatric trauma, pediatric tumors, evaluation of solid abdominal parenchymal organ masses, suspected abscess, or inflammatory disorders.[34] Specifically, MDCT is increasingly used in the evaluation of children with abdominal pain, particularly in patients with suspected appendicitis.[35] Callahan and colleagues used MDCT in the evaluation of children with appendicitis and reduced the total number of hospital days, negative laparotomy rate, and cost per patient.[36] In addition, MDCT may be useful in identifying alternative diagnoses, including other bowel pathologies, ovarian pathologies, and urinary tract pathologies (Fig. 4-4).[35]

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 which urolithiasis is suspected.[35] CT findings of urolithiasis include visualization of the radiopaque stone, dilatation of the ureter

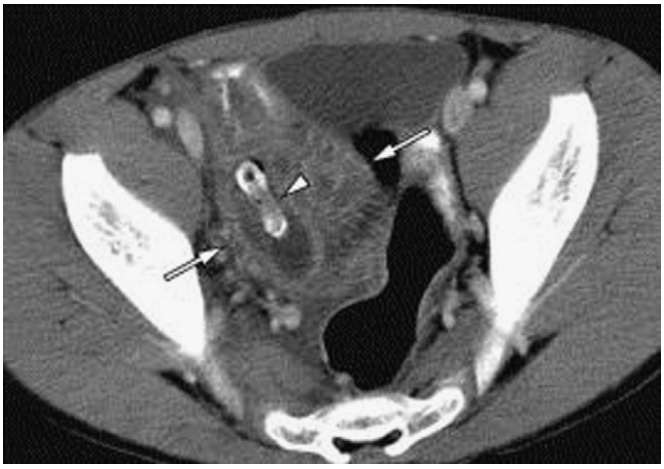


FIGURE 4-4 Multidetector computed tomography of an 8-year-old boy with appendicitis. The *arrows* point to an inflammatory mass in the right lower quadrant with a possible appendicolith *(arrowhead)*. (From Donnelly LF, Frush DP: Pediatric multidetector body CT. Radiol Clin North Am 2003;41:637–655.)

or collecting system, asymmetric enlargement of the kidney, and perinephric stranding.[35] Of note, MDCT evaluation of these patients usually requires a noncontrast study. Another area in which CT is showing increased use is for the evaluation of children with IBD.[35] In these patients, CT may be superior to fluoroscopy for demonstrating inflammatory changes within the bowel as well as extraluminal manifestations of IBD, such as peribowel inflammatory change or abscess.[35]

In the chest, MDCT is used for the evaluation of infection and complication of infections, as well as cancer detection and surveillance. Evaluation of congenital abnormalities of the lung, mediastinum, and heart are also indications. In particular, MDCT may be useful in the assessment of bronchopulmonary foregut malformations in which sequestration is a consideration.[34] Similarly, the use of MDCT in the evaluation of the pediatric cardiovascular system has been particularly valuable.[37] 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 evaluation of patients with pectus malformations, because it allows for lower doses of radiation.[35]

Three-Dimensional Computed Tomography

The advent of helical CT and MDCT has enabled the postacquisition processing of individual studies for the creation of three-dimensional CT image reconstructions. These 3D reconstructions are valuable in the preoperative planning of complex surgical procedures. Although 3D CT imaging has been possible for almost 25 years, the quality, speed, and affordability of these techniques have only recently improved enough to result in their incorporation into routine clinical practice.[38] Currently, four main visualization techniques are used in CT reconstruction labs to create 3D CT images. These include multiplanar reformation, maximum intensity projections, shaded surface displays, and volume rendering. Multiplanar reformation and maximum intensity projections are limited to external visualization, while shaded surface displays and volume rendering allow immersive or internal visualization, such as virtual endoscopy.[33]

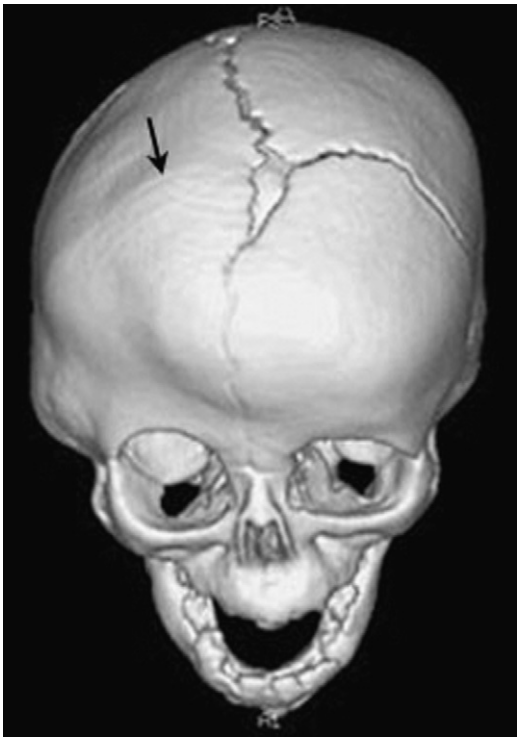


FIGURE 4-5 3D computed tomography reconstruction of an infant skull showing premature closure of the right coronal suture. (From Rubin GD: 3-D imaging with MDCT. Eur J Radiol 2003;45(Suppl 1):S37–S41.)

Three-dimensional CT has been beneficial in the preoperative planning of pediatric craniofacial, vascular, and spinal operations. Specifically, 3D CT has been used to evaluate maxillofacial fractures[39] and craniofacial abnormalities, as well as vascular malformations. Figure 4-5 illustrates a 3D CT reconstruction of an infant with craniosynostosis. Similarly, 3D CT has been reported useful in the planning of hemivertebra excision procedures for thoracic and thoracolumbar congenital deformities.[40] A particularly interesting application of 3D CT is the creation of "virtual endoscopy" images for the interior surface of luminal structures, such as the bowel, airways, blood vessels, and urinary tract.[33] In particular, virtual endoscopy using 3D CT may be useful in the diagnosis of small bowel tumors, lesions that are often difficult to detect using standard modalities (Fig. 4-6).[38]

Electron Beam Computed Tomography

Introduced clinically in the 1980s, electron beam computed tomography (EBCT) scanners are primarily used in adult cardiology to image the beating heart. As opposed to traditional CT scanners, EBCT systems do not use a rotating assembly consisting of an x-ray source directly opposite an x-ray detector. Instead, EBCT scanners use a large, stationary x-ray tube that partially surrounds the imaging field. The x-ray source is moved by electromagnetically sweeping the electron beam focal point along an array of tungsten anodes positioned around the patient. The anodes that are hit emit x-rays that are collimated in a similar fashion to standard CT scanners. Because this is not mechanically driven, the movement can be very fast. In fact, EBCT scanners can acquire images up to 10 times faster than helical CT scanners. Current EBCT systems are capable of performing an image sweep in 0.025 seconds compared with the 0.33

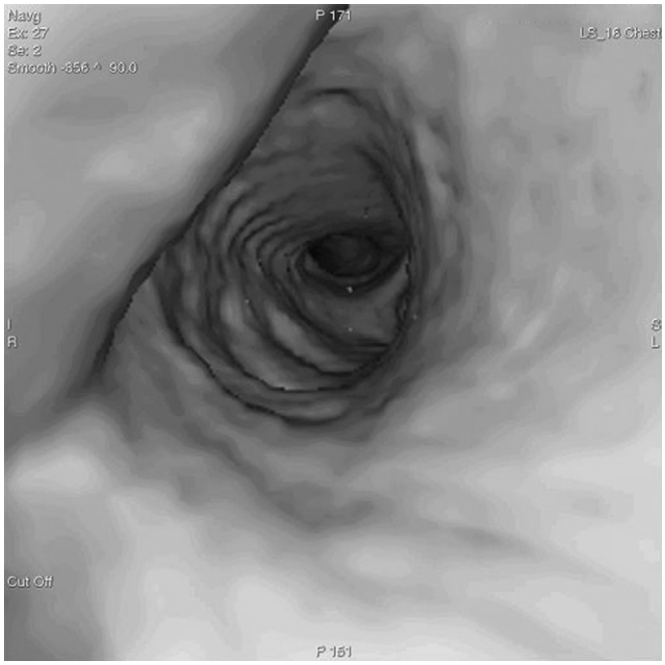


FIGURE 4-6 Virtual colonoscopy.

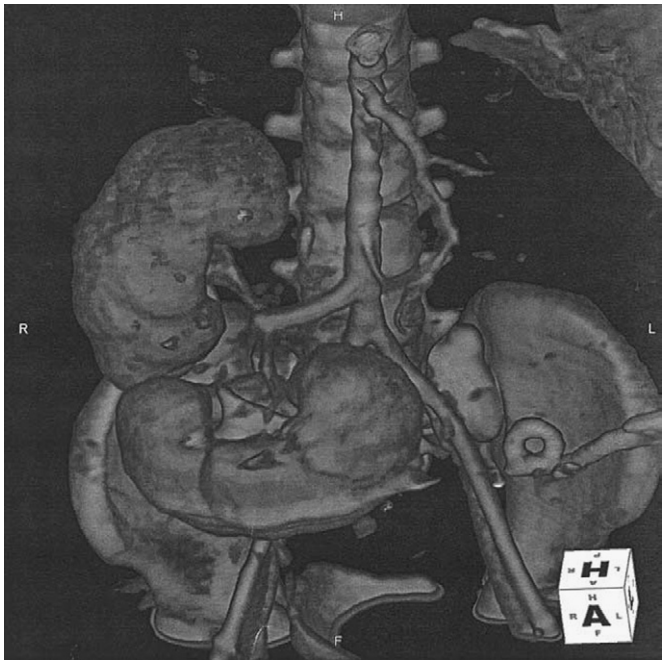


FIGURE 4-7 Electron beam computed tomography of transplanted kidney. (From Talisetti A, Jelnin V, Ruiz C, et al: Electron beam CT scan is a valuable and safe imaging tool for the pediatric surgical patient. J Pediatr Surg 2004;39:1859–1862.)

seconds for the fastest mechanically swept CT systems. This rapid acquisition speed minimizes motion artifacts, enabling the use of EBCT scanners for imaging the beating heart. In addition to faster image acquisition times resulting in decreased motion artifacts, EBCT scanners generally result in a 6- to 10-fold decrease in radiation exposure compared with traditional CT scanners.

To date, EBCT scanners have not yet seen widespread adoption. The systems are necessarily larger and more expensive than helical CT scanners. Advances in multidetector helical CT scan designs have enabled cardiac imaging using standard, mechanically driven systems.

The use of EBCT in the pediatric population has primarily been reported for the imaging of cardiac anomalies.[41,42] However, as we increasingly understand the risks associated with ionizing radiation exposure in children, the decreased exposure associated with EBCT systems appears attractive. In addition, the faster acquisition times and minimization of motion artifact could theoretically result in decreased sedation requirements in young patients. Talisetti and colleagues reported the use of EBCT to evaluate several pediatric surgical patients—one patient with thoracic dystrophy and an abdominal wall hernia, one patient with ascites status postrenal transplant (Fig. 4-7), and several patients with renal and pelvic tumors.[43] In their report, they highlighted the potential advantages of decreased radiation exposure and sedation requirements associated with EBCT systems.

MAGNETIC RESONANCE IMAGING

The first MRI examination on a human was performed in 1977 by Dr. Raymond Damadian, with colleagues Dr. Larry Minkoff and Dr. Michael Goldsmith. This initial exam took 5 hours to produce one, relatively poor quality image. Since then, technological improvements have increased the resolution and speed of MRI. Today, MRI is able to provide unparalleled noninvasive images of the human body. In addition, newer MRI systems now allow images to be obtained at subsecond intervals, facilitating fast, near real-time MRI. Similarly, new MRI techniques are now being developed to provide functional information on the physiologic state of the body. This section will provide a brief overview of MRI, focusing on recent technologic advances, such as *ultrafast MRI, higher field strength MRI systems, motion artifact reduction techniques,* and *functional MRI*.

MRI creates images by using a strong, uniform magnetic field to align the spinning hydrogen protons of the human body. A radiofrequency (RF) pulse is then applied, causing some of the protons to absorb the energy and spin in a different direction. When the RF pulse is turned off, these 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 using mathematical algorithms.

Higher Field Strength MRI Systems

Over the last decade, MRI has advanced significantly with the transition from 1.5 Tesla (T) to 3.0 T field strength systems (Fig. 4-8). Using higher magnetic field strength, 3.0 T systems demonstrate improved image resolution, faster image acquisition speeds, and improved fat suppression.[44] In addition, 3.0 T systems theoretically enable a twofold increase in signal-to-noise ratio (SNR) compared with 1.5 T systems as SNR increases linearly with field strength. This is particularly important for imaging smaller patients with anatomical structures. Although 3.0 T systems are rapidly becoming the standard in pediatric MRI imaging, ultrahigh field strength 7.0 T systems are currently being evaluated. These systems

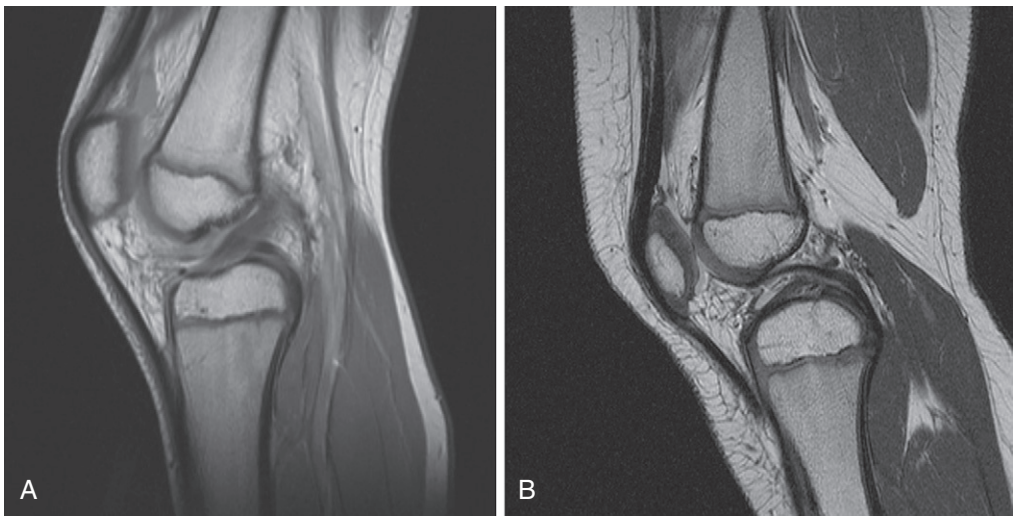


FIGURE 4-8 Comparison of image quality between 1.5 T (**A**) and 3.0 T (**B**). (From MacKenzie JD, Vasanawala SS: Advances in pediatric MR imaging. Magn Reson Imaging Clin N Am 2008;16:385–402.)

potentially provide the same advantages listed above but to a higher degree. Disadvantages include higher deposition of radiofrequency energy, magnification of artifacts, and more challenging hardware and software design. Although still under investigation, ultrahigh field strength MRI may enable unique studies such as sodium imaging, which can be used to monitor renal physiology and function, myocardial viability, and phosphorous imaging, which has been suggested as a method of evaluating organ pH and cancer metabolism.[44]

Ultrafast MRI

The first major development in high speed MRI occurred in 1986 with the introduction of the gradient-echo pulse sequence technique (GRE). This technique decreased practical scan times to as little as 10 seconds. In addition to increasing the patient throughput of MRI scanners, the faster scan times significantly increased the application of MR imaging in body regions (e.g., the abdomen) where suspended respiration could eliminate most motion-related image distortions.[45,46] Since then, GRE techniques have undergone iterations and further developments, such as balanced steady-state imaging, achieving subsecond level scan times.

More recently, parallel imaging (or parallel MRI) has emerged as a method of increasing MRI imaging speed. Parallel imaging techniques are able to construct images using reduced data sets by combining the signals of several coil elements in a phased array. In this manner, higher imaging speeds are achievable, generally allowing speed increases of two- to threefold.[44] In addition, MRI parallel imaging results in improved signal-to-noise ratio, thereby decreasing artifact and improving image quality.

The high speed of ultrafast MRI represents a significant advantage in the care of children. Most traditional MR protocols require 30 to 40 minutes of table occupancy. During this time the patient must remain still to avoid motion artifact.[47] For many children, this often requires sedation, general anesthesia, and even muscular blockade to enable them to remain motionless long enough for a quality study to be completed. This is obviously a significant impediment toward the widespread use of MRI in children. Ultrafast MRI significantly reduces this requirement, 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.[48]

Ultrafast MRI also significantly reduces the motion artifacts that occur in the abdomen and thorax resulting from normal respiratory and peristaltic movements. In particular, the smearing artifact associated with the use of oral contrast agents during MR imaging of the intestinal tract had previously decreased image quality.[49] Using GRE and parallel imaging techniques, modern MRI can achieve scan times that are fast enough to be completed during a breath hold and are fast relative to normal abdominal motion.[44] In addition, by decreasing motion artifact and enabling fast image acquisition, ultrafast MRI protocols enable the practical application of cardiac MRI and fetal MRI.[50] Similarly, volumetric or 3D MRI has become practically feasible in children with ultrafast MRI techniques that decrease the acquisition time required for these data intensive studies.[44]

Motion Artifact Reduction Techniques

Motion artifacts may be secondary to physiologic movement (cardiac, respiratory, and peristaltic) as well as voluntary movement. This is particularly significant in pediatric patients. Recently, several techniques have been used to minimize motion artifacts. One broad method employs high-speed image acquisition as detailed above. Another method is navigation imaging where extra navigator echoes are used to detect image displacements. These displacements are used to reject or correct data reducing artifacts.[44] Currently, navigation imaging has been applied to cardiac imaging and hepatobiliary imaging to reduce motion artifacts caused by respiratory movement. Similarly, PROPELLER (periodically rotated overlapping parallel lines with enhanced reconstruction) imaging is a method for reducing motion artifacts by signal averaging successive rotating samples of data.

Functional Magnetic Resonance Imaging

Functional magnetic resonance imaging (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 more than 15 years ago, fMRI has seen widespread clinical and research application in the adult

population. Functional MRI is founded on two basic physiologic assumptions regarding neuronal activity and metabolism. Specifically, fMRI assumes that neuronal activation induces an increase in local glucose metabolism, and that this increased metabolic demand is answered by an increase in local cerebral blood flow.[51] 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.[52] BOLD imaging takes advantage of small differences in the magnetic properties of oxygenated and deoxygenated hemoglobin. Since 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.[51]

Functional magnetic resonance imaging requires significant subject preparation in order to prepare the child to lie still in the scanner for the duration of the study. Various preparation techniques have been described that decrease the anxiety and uncertainty that a child might experience regarding the study. These include presession educational videos, presession tours with members of the radiology staff, and presession practice runs. Optimally, fMRI studies require a nonsedated, cooperative patient to assess functional neuronal activity. However, it has been recently shown that passive range of motion may activate the sensorimotor complex in sedated patients. This may enable functional motor mapping in patients who are unable to cooperate with active tasks.[53]

At this time, the use of fMRI in the pediatric population is still at the earliest stages. However, fMRI holds tremendous promise in the evaluation of central nervous system (CNS) organization and development, characterization of brain plasticity, and the evaluation and understanding of neurobehavioral disorders.[51] In addition, current clinical applications of fMRI include the delineation of eloquent cortex near a space-occupying lesion and the determination of the dominant hemisphere for language. fMRI is also used to map the motor cortex. These clinical applications are designed to provide preoperative functional information for patients undergoing epilepsy or tumor surgery.[53] This information can be used to guide resection and to predict postoperative deficits.[53]

Fetal Magnetic Resonance Imaging

Magnetic resonance imaging has become an increasingly used imaging modality for the evaluation of fetal abnormalities. Rapid image acquisition times and motion artifact reduction techniques allow for effective imaging studies despite fetal movement. Although US remains the primary modality for imaging the unborn fetus, fetal MRI has demonstrated several distinct advantages. In addition to providing fine anatomic detail, fetal MRI is not limited by maternal obesity, fetal position, or oligohydramnios—all factors that can limit the effectiveness of US evaluation.[54] The use of fetal MRI to characterize fetal CNS, thoracic, abdominal, genitourinary, and extremity anomalies has been well described. Particularly relevant to the field of pediatric surgery, fetal MRI has been used to assist in the prenatal differentiation between enteric cysts and meconium pseudocysts. Similarly, fetal MRI is used to characterize the nature and origin of abdominal masses and to evaluate fetal tumors.[54] Such information may be valuable for prenatal counseling and decision making as well as for preoperative planning. As the field of fetal surgery matures, fetal MRI may become increasingly useful in the evaluation of abnormalities amenable to fetal intervention.

POSITRON EMISSION TOMOGRAPHY IMAGING

Positron emission tomography, or PET, is an increasingly used imaging technology that provides information on the functional status of the human body. First developed in 1973 by Edward Hoffman, Michael Ter-Pogossian, and Michael Phelps at Washington University, PET imaging is now one of the most commonly performed nuclear medicine studies in the United States.[55] Although CT, MRI, and US imaging techniques provide detailed information regarding the anatomic state of a patient, PET imaging provides information on the current metabolic state of the patient's tissues. In this manner, PET imaging 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.[56] These radionuclides are created by bombarding target material with protons that have been accelerated in a cyclotron.[56] These positron-emitting radionuclides are then used to synthesize radiopharmaceuticals that are part of biochemical pathways in the human body.[56] The most commonly used example of this is the use of the fluorinated analog of glucose, 2-deoxy-2-(18)F-fluoro-D-deoxyglucose (FDG).[57] Like glucose, FDG is phosphorylated by the intracellular enzyme hexokinase. In its phosphorylated form, FDG does not cross cell membranes and therefore accumulates within metabolically active cells. In this manner, PET imaging using FDG provides information about the glucose use in different body tissues.[57]

In order to be detected, FDG is synthesized using ^{18}F, a radioisotope with a half-life of 110 minutes.[57] 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 through a carbon foil. The resultant high-energy protons are then directed toward a target chamber that contains stable ^{18}O enriched water.[56] The protons undergo a nuclear reaction with the ^{18}O enriched water to form hydrogen ^{18}F fluoride. The reaction is detailed in the equation that follows.[56]

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

^{18}F is an unstable radioisotope that decays by beta-plus emission or electron capture and emits a neutrino (ν) and a positron (β^+).[56] The emitted positrons are then annihilated with electrons to release energy in the form of photons, which are detected by modern PET scanners and are the basis of PET imaging. 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.[56] Because PET scanning uses unstable radioisotopes, PET probes must be synthesized immediately prior to a PET study. This 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).[57]

In a typical PET study, the radiopharmaceutical agent is systemically administered to the patient by intravenous injection. The patient is then imaged by the PET scanner, which measures the radioactivity (photon emission as above) throughout the body and creates 3D pictures or images of tissue function. Currently, PET imaging is used extensively for the accurate evaluation and monitoring of tumors of the lung, colon, breast, lymph nodes, and skin.[58] PET imaging is used to facilitate tumor diagnosis, localization, and staging; monitoring of antitumor therapy; tumor tissue characterization; radionuclide therapy; and screening for tumor recurrence.[59] Though nonspecific, FDG is often used because malignant cells generally display increased glucose use with up-regulation of hexokinase activity.[56]

PET imaging has also been used to assess the activity of noncancerous tissues to provide information on their viability or metabolic activity. In adults, PET scans are used to determine the viability of cardiac tissue in order to decide whether a patient would benefit from coronary bypass grafting.[60,61] Recently, this application was extended to the pediatric population in order to assess cardiac function after arterial switch operations with suspected myocardial infarction.[62] Similarly, PET scans can be used to visualize viability of brain tissue in order to make prognostic determinations after stroke.[63] Finally, PET imaging is used to identify regions of abnormal activity in brain tissue, helping to localize seizure foci or diagnose functional disorders, such as Parkinson disease and Alzheimer disease.[64,65]

Though PET imaging provides important functional information regarding the metabolic activity of human tissues, it often provides relatively imprecise images compared with traditional anatomic imaging modalities. This is in large part because of the physics of PET as an imaging modality. Specifically, the positrons emitted by radionuclides, such as FDG, generally have enough kinetic energy to travel a small distance before annihilating with an electron.[56] This distance is called the *mean positron range* and varies depending on tissue density. The difference in position between the initial location of the positron and its site of annihilation results in positron range blurring. This limits the spatial resolution of PET imaging, which is typically considered to be approximately 5 mm using current scanners.[56] *Noncollinearity* or variation in the path of emitted photons other than the expected 180 degrees, also contributes to decreased spatial resolution in PET imaging. Because of these limitations, PET imaging is often useful for highlighting areas suspicious for malignancy but may be difficult to use during preoperative planning, because it does not accurately correlate the area of suspicion with detailed anatomic information.[58]

Recently, combined PET/CT scanners have been developed that simultaneously perform PET scans and high resolution CT scans. Introduced 10 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 (Fig. 4-9).[57] Prior to the availability of PET/CT scanners, CT and PET scans of the same patient acquired on different scanners at different times were often aligned using complex, labor-intensive algorithms.[57] However, other than for brain imaging, these algorithms often failed to adequately fuse the studies. In contrast, combined PET/CT scanners rely on hardware fusion and not solely software manipulation and do not suffer these limitations.

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.[66,67] Currently, the clinical application of combined PET/CT imaging in the pediatric population has not been extensively studied. However, the combination of functional information with fine anatomic data provides obvious advantages with regard to surgical planning and will therefore likely play a large role in surgical practice.

MOLECULAR IMAGING

Ultrasonography, CT, MRI, and PET imaging represent established technologies that are commonly used in the care of pediatric patients around the world. 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 classical imaging modalities, a new field termed "molecular imaging" sets forth to probe the molecular abnormalities that are the basis of disease rather than to image the end effects of these alterations.[68] Molecular imaging is a rapidly growing research discipline that combines the modern tools of molecular and cell biology with noninvasive imaging technologies. 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 those pathways that are key targets in specific disease processes. The development and application of molecular imaging will someday directly affect patient care by elucidating the molecular processes underlying disease and lead to the early detection of molecular changes that represent "predisease" states.[69]

Molecular imaging can be defined as "the in vivo characterization and measurement of biologic processes at the cellular and molecular level."[68] From a simplistic standpoint, molecular imaging consists of two basic elements:

1. Molecular probes whose concentration, activity and/or luminescent properties are changed by the specific biologic process under investigation[69]
2. A means by which to monitor these probes[69]

Currently, most molecular probes are either radioisotopes that emit detectable radioactive signals or light- or near-infrared (NIR)–emitting molecules.[69] These probes are considered either direct binding probes or indirect binding probes.[70] Radiolabeled antibodies designed to facilitate the imaging of cell-specific surface antigens or epitopes are commonly used examples of direct binding probes.[70] Similarly, radiolabeled oligonucleotide antisense probes developed to specifically hybridize with target messenger RNA (mRNA) or proteins for the purpose of direct, in vivo imaging are more recent examples.[70] Radiolabeled oligonucleotides represent complimentary sequences to a small segment of target mRNA or DNA, allowing for the direct imaging of endogenous gene

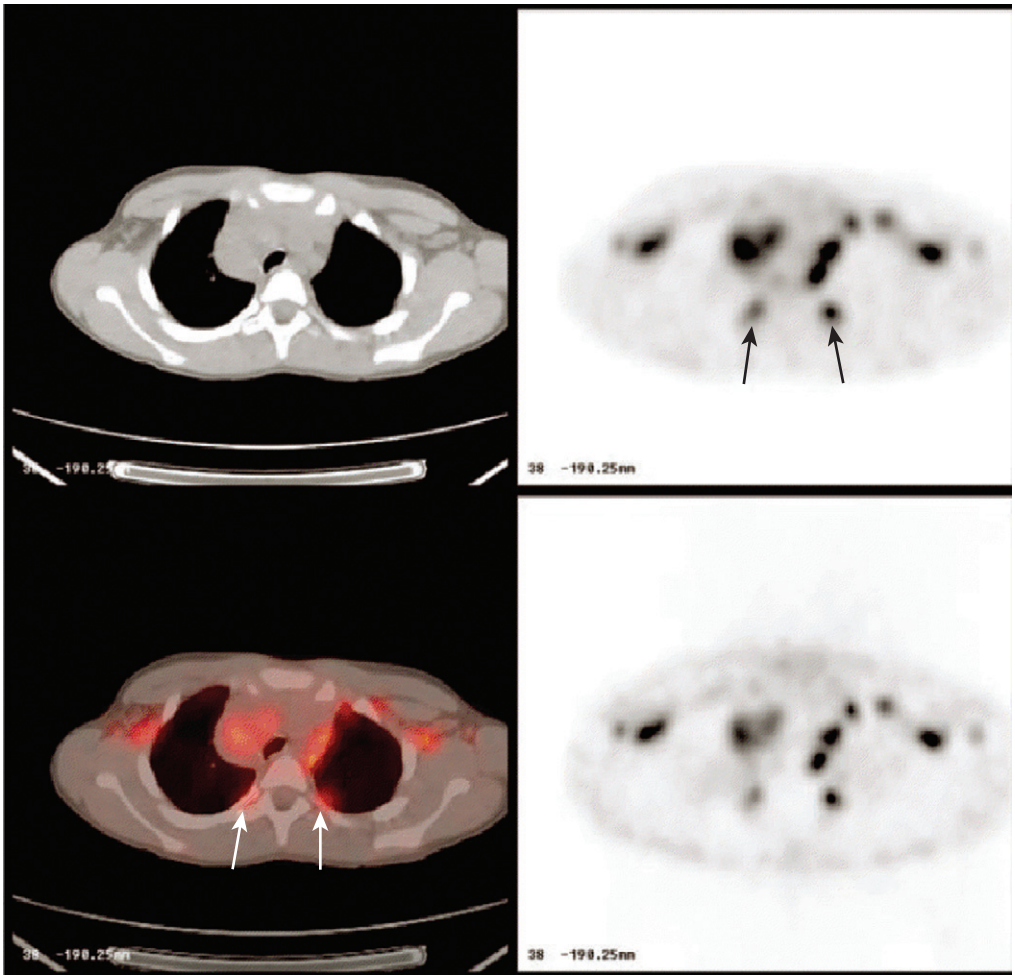


FIGURE 4-9 Combined positron emission tomography (PET)-CT images (axial) through the upper chest of a 7-year-old girl with a mediastinal mass found to be a necrotizing granuloma. Multiple sites of 2-deoxy-2-(18)F-fluoro-D-deoxyglucose (FDG)–avid axillary lymph nodes and multiple foci within the mediastinal mass are visualized. Arrows highlight the symmetric avidity of the costovertebral junctions for FDG that can be seen in children. (From Kaste SC: Issues specific to implementing PET-CT for pediatric oncology: What we have learned along the way? Pediatr Radiol 2004;34:205-213.) *(See Expert Consult site for color version.)*

expression at the transcriptional level.[70] Finally, positron-emitting analogs of dopamine, used to image the dopamine receptors of the brain, are other examples of direct binding probes.[69]

Although direct binding probes assist in the imaging of 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 is used for neurologic, cardiovascular, and oncology investigations.[69] Systemically administered FDG is accessible to essentially all tissues.[69]

The use of reporter transgene technology is another powerful example of molecular imaging with indirect binding probes. Reporter genes are nucleic acid sequences encoding easily assayed proteins. Such reporter genes have been long used in molecular biology and genetics studies to investigate intracellular properties and events, such as promoter function/strength, protein trafficking, and gene delivery. Using molecular imaging techniques, reporter genes have now been used to analyze gene delivery, immune cell therapies, and the in vivo efficacy of inhibitory mRNAs in animal models.[71] In vivo bioluminescent imaging using the firefly or *Rinella* luciferase or fluorescent optical imaging using green fluorescent protein (GFP) or DsRed are optical imaging examples of this technique (Fig. 4-10).[72,73] Recently, semiconductor quantum dots have been used in fluorescent optical imaging studies. Although fluorescent proteins are limited in their number of available colors, quantum dots can fluoresce at different colors over a broad region of the spectrum by altering their size and surface coating. To date, the quantum dots that have been tested with in vivo experimental models include amphiphilicpoly (acrylic acid), short-chain (750 D) methoxy-PEG and long-chain (3400 D) carboxy-PEG quantum dots, and long-chain (5000 D) methoxy-PEG quantum dots.[74]

In the field of immunology and immunotherapy research, Costa and colleagues transduced the autoantigen-reactive CD4+ T-cell population specific for myelin basic protein (MBP) with a retrovirus that encoded a dual reporter protein composed of GFP and luciferase, along with a 40 kD monomer of interleukin-12 as a therapeutic protein.[75] Bioluminescent imaging (BLI) techniques were then used to monitor the migratory patterns of the cells in an animal model of multiple sclerosis. BLI demonstrated that the immune cells that would typically cause destruction of myelin trafficked to the central nervous system in symptomatic animals. Furthermore, they

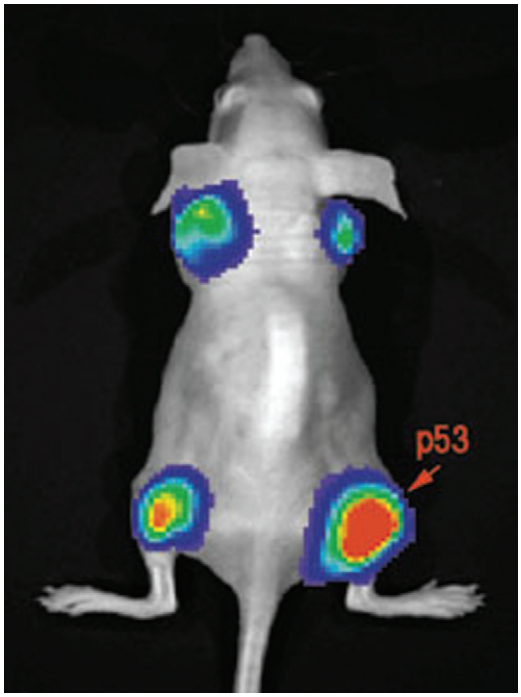


FIGURE 4-10 Nude mouse carrying a wild-type *TP53*-expressing human colon xenograft with a stably integrated *TP53*-responsive luciferase reporter gene. Injection of exogenous *TP53* expressed by an adenovirus vector led to detectable increase in luciferase activity within an established tumor *(arrow)*. (From Wang W, El-Deiry WS. Bioluminescent molecular imaging of endogenous and exogenous p53-mediated transcription in vitro and in vivo using an HCT116 human colon carcinoma xenograft model. Cancer Biol Ther. 2003 Mar-Apr;2(2):196-202.) *(See Expert Consult site for color version.)*

found that CD4 T-cell expression of the IL-12 immune modulator resulted in a clinical reduction in disease severity.[75]

Similarly, Vooijs and colleagues generated transgenic mice in which activation of luciferase expression was coupled to deletion of the retinoblastoma (*Rb)* tumor suppressor gene.[76] Loss of *Rb* triggered the development of pituitary tumors in their animal model, allowing them to monitor tumor onset, progression, and response to therapy in individual animals by repeated CCD (charged coupled device) imaging of luciferase activity.[76] 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, allowing for PET-, SPECT- (single-photon emission tomography), or MRI-based molecular imaging.[70]

The second major element of molecular imaging is the imaging modality/technology itself. Direct and indirect binding probes can be radiolabeled to allow nuclear-based in vivo imaging of a desired cellular/molecular event or process using PET or SPECT imaging. In fact, micro-PET and micro-SPECT systems have been developed specifically for molecular imaging studies in animal models.[68] Similarly, optical imaging techniques, such as bioluminescent imaging, near-infrared spectroscopy, and visible light imaging using sensitive CCDs 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.[68]

At this time, the field of molecular imaging is largely an experimental one, with significant activity in the laboratory and little current clinical application. Molecular imaging research is largely focused on investigating the molecular basis of clinical disease states and their potential treatments, including mechanisms surrounding apoptosis, angiogenesis, tumor growth and development, and gene therapy.[68]

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 advancement that allows the simultaneous assay of thousands of genes.[77] Microarray technology has been applied to redefine 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*.

Innovative Therapeutics: Technologies and Techniques

A surgical operation requires two key elements: an "image," or more broadly, information regarding the anatomy of interest, and a "manipulation" of the patient's tissue with the goal of a therapeutic effect. Classically, the "image" is obtained through the eyes of the surgeon and the "manipulation" is performed using the surgeon's hands and simple, traditional surgical instruments. During the last 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 or through a flexible endoscope or laparoscope. This endoscope may be monocular or binocular, providing 2D or 3D visualization. These technologies provide the surgeon with high-quality, magnified images of anatomical areas that may be inaccessible to the naked eye. Similarly, a surgical "manipulation" of tissue and organs may be accomplished using a catheter, flexible endoscope, or longer laparoscopic instruments. Furthermore, devices such as staplers, electrocautery, ultrasonic energy tools, and radiofrequency emitters are all used to manipulate and affect tissue with a therapeutic goal. These technologies have changed the way surgical procedures are performed, enabling and even creating 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. These include 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

Handheld energy devices designed to provide hemostasis and ablate tissue are some of the most widely used surgical technologies throughout the world. Since the first reports of

electrosurgery in the 1920s,[78] multiple devices and forms of energy have been developed to minimize blood loss during tissue dissection. These instruments, including monopolar and bipolar electrocautery, ultrasonic dissectors, argon beam coagulators, cryotherapy, and infrared coagulators, are used in operating rooms on a daily basis. In addition, improvements to these tools and their techniques or use are continually being developed.

Electrocautery

The application of high-frequency alternating current is now known variously as electrocautery, electrosurgery, or simply "the Bovie." Although the concept of applying an electrical current to living tissue was reported as far back as the late sixteenth century, the practical application of electrocautery in surgery did not begin to develop until the early 1900s. In 1908, Lee de Forest developed a high-frequency generator that was capable of delivering a controlled cutting current. However, this device used expensive vacuum tubes and therefore saw very limited clinical application. In the 1920s, W.T. Bovie developed a low-cost spark-gap generator. The potential for using this device in surgery was recognized by Harvey Cushing during a demonstration in 1926, and the first practical electrosurgery units were in use soon thereafter.[78]

Monopolar electrocautery devices deliver the current through an application electrode through the patient's body returning to a grounding pad. Without a grounding pad, the patient would suffer a thermal burn injury wherever the current sought 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, in order to generate heat efficiently, and the returning electrode is large, to broadly disperse energy. There are three other settings that 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 "coag" mode, the device generates less heat at a slower frequency with larger lateral thermal spread. Consequently, 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.

Recently, advanced bipolar devices use a combination of pressure and bipolar electrocautery to seal tissues. These devices then use a feedback-controlled system that automatically stops the energy delivery when the seal cycle is complete. The tissues are then divided sharply within the sealed zone. Advanced bipolar devices are capable of sealing blood vessels up to 7 mm in diameter, with the seal reportedly capable of withstanding 3 times normal systolic blood pressure. Examples of this class of device include the LigaSure distributed by Covidien (Mansfield, Mass.) and the ENSEAL device distributed by Ethicon Endosurgery (Cincinnati, Ohio).

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 through the argon gas and produces thermal coagulation. The flow of the argon gas improves visibility and disperses any surface blood, enhancing coagulation. Its applications in hepatic surgery are unparalleled.

Surgical Lasers

Lasers (*L*ight *A*mplification by *S*timulated *E*mission of *R*adiation) 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 tends to be minimal, and critically, the laser can be delivered through a fiber optic system.

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

Photodynamic Therapy

A novel use 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, leading to tissue destruction. Applications have been widespread.[79] Metaplastic cells, in particular in Barrett esophagus, may also be susceptible.[80]

Ultrasonography

In addition to the diagnostic use of US at low frequency, the 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 (ESWL). The focused energy produces a shock wave resulting in fragmentation of the stones to a size that can be spontaneously passed.

When high-intensity focused US (HIFU) energy from multiple beams is focused at a point on a target tissue, heating and thermal necrosis results. None of the individual ultrasonic beams is of sufficient magnitude to cause injury, only at the focus point does thermal injury result. Thus subcutaneous nodules may be targeted without injury to the 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, thus limiting utility.

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.

Cavitation Devices

The CUSA, a cavitation ultrasonic 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. The application of this energy source heats the target tissue, causing protein denaturization and necrosis. A feedback loop sensor discontinues the current at a selected point, minimizing collateral damage. Its targeted use in modulating the lower esophageal sphincter for the treatment of reflux has been reported.[81]

Microwave Energy

Microwave energy (2,450 MHz) can be delivered by 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 with 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-GUIDED THERAPY

In recent years, ultrasonography, computerized tomography, and magnetic resonance imaging have expanded beyond their role as mere diagnostic modalities, and are now the foundation of sophisticated interactive computer applications that directly guide surgical procedures.[3,82,83] 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 graphical 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, creating new opportunities for real-time, interactive computer applications during surgical procedures.[77–80] This area of development, termed image-guided surgery, has slowly evolved into a field best called *information-guided therapy* (IGT), reflecting 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 use 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 application of relevant information sources.

Significance

As stated in the National Institutes of Health 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 the considerable clinical interest in the well-recognized benefits of minimal access surgery (MAS), 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 is of utmost importance.

Patient-specific image data sets such as CT or MRI, when correlated with fixed anatomic reference points (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 directionality. Thus the addition of CAS provides the advantages of MAS with the added benefits of greater precision and the increased likelihood of complete and accurate resections. The junction between CAS and MAS presents research opportunities and challenges for both imaging scientists and surgeons.

General Requirements

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

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 An American Association of Neurosurgeons survey of 250 neurosurgeons[57] disclosed that surgeons had little tolerance for error (1–2-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 given to errors associated with intraoperative tissue deformation.

Repeatability and Robustness Image-guided therapy 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 critical area of interest to biomedical engineers and is especially critical for compensation of tissue deformation. Whether produced by microscopes, endoscopes, fluoroscopes, electrical recordings, physiological 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 the details of the computational model.

Ultrasound Image-Guided Therapy

Compared with adults, children have excellent US image resolution because of minimal subcutaneous tissue. Furthermore, the lack of ionizing radiation, fast procedure times, relatively low cost, as well as its real-time and multiplanar imaging capabilities, make US especially attractive in the pediatric population. US is the most accessible advanced imaging tool that surgeons can currently use independently. Intraoperative applications include using it as an aid to vascular access, intraoperative tumor localization and resection, and drainage procedures.[84–87]

Computed Tomography and Magnetic Resonance Image-Guided Therapy

Computed tomography and magnetic resonance imaging are not widely used by surgeons without the involvement of radiologists. Although CT-based IGT offers excellent visualization that is not limited by the presence of air or bone, its use in the pediatric population has been limited by concern for the downstream effects of ionizing radiation.[88,89] In addition, there are limited imaging planes, poor differentiation of some lesions related to less fat in babies and children, as well as longer procedure times and greater costs than for US intervention. Nonetheless, CT-guided therapeutic interventions, such as lung and bone biopsies or drainage of deep fluid collections, are routinely done, particularly now that radiation exposure can be reduced with pulsed or intermittent fluoroscopic techniques and dedicated pediatric CT parameters.[82]

The advantages of MRI as a guiding tool include exquisite soft tissue detail, multiplanar real-time imaging, and the ability to assess physiologic and functional parameters (temperature, flow, perfusion).[82,90] Traditional interventional MRI units include an opening that allows easy access to the patient. These units have relatively low field strength, however, which results in poorer image resolution. Higher field strength magnets are now preferred, albeit at the cost of decreased patient accessibility and the requirement of nonferromagnetic instruments. To date, the majority of pediatric applications of MRI-guided therapy have been in the field of neurosurgery. Common applications include tumor ablation/resection or biopsy.[90,91] Currently, there are no data on MRI-guided abdominal interventions in the pediatric population. In 2005, Schulz and colleagues[90] reviewed indications for MR-guided interventions in children. They determined that MR-guided imaging is not a reliable method for chest interventions. They also suggested that the primary use of intraoperative MRI will be for lesions in particularly difficult-to-access areas with nonpalpable findings, such as intracranial and skull base tumors. Future potential applications of MRI include endovascular procedures[91] and thermal ablation of tumors.

Navigational systems establish the relationship between the surgeon's movements and image-based information. They enable the use of preoperative imaging for precise intraoperative localization and resection of lesions using an exact navigation pathway. Neuronavigation systems provide this precise surgical guidance by referencing a coordinate system of the brain with a parallel coordinate system of the three-dimensional image data of the patient.[92,93] These data are displayed on the console of the computer workstation so that the medical images become point-to-point maps of the corresponding actual locations within the brain. The spatial accuracy of these systems is further enhanced by the use of intraoperative MRI that provides real-time images to document the residual lesion and to assess for brain shift during surgery.[94] The precision (error rates of 0.1 to 0.6 mm) provided by neuronavigation systems enables minimal access neurosurgical procedures, significantly reducing morbidity for both adult and pediatric patients.[95] Neuronavigation has not yet been successfully deployed for abdominal surgery. The inability to simply transfer the methodology from neurosurgery is mainly a result of intraoperative organ shifting and corresponding technical difficulties in the online applicability of presurgical cross-sectional imaging data. Furthermore, it remains unclear whether 3D planning and interactive planning tools will increase precision and safety of abdominal surgery.

Radiotherapy and Fractionation

The field of radiation oncology represents perhaps the most mature example of IGT. 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, very soon after Roentgen's discovery of x-rays in 1895.[96] In the 1930s, Coutard described the practice of "fractionation," [96] which refers to the division of a total dose of radiation into multiple smaller doses, typically given on a daily basis. Fractionation is a bedrock principle that underlies the entire field of radiotherapy.[97,98] 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. By fractionating the therapy, normal tissue should be allowed to recover while pathologic tissue is destroyed. Though fractionation regimens differ depending on specific pathology, current regimens often involve up to 30 treatments.[96]

Stereotactic Radiosurgery

Stereotactic radiosurgery refers to the method and corresponding technology for delivering a single high dose of ablative radiation to target tissue using precision targeting and large numbers of cross-fired highly collimated beams of high-energy ionizing radiation. Conceptualized in the 1950s by Swedish neurosurgeon Lars Leksell, this technology has been used to treat/ablate a variety of benign and malignant intracranial lesions without any incision.[99] Leksell showed that there was an exponential relation between dose and the time during which necrosis developed.[96]

Most recently, radiosurgical techniques are being applied toward the treatment of extracranial diseases, including spinal tumors and lesions of the thoracic and abdominal cavities.[100,101] Many of the newest applications of stereotactic radiosurgery fall under the traditional realm of general surgery, including lung, liver, and pancreatic cancers. The lesioning of normal brain tissue, such as the trigeminal nerve (trigeminal neuralgia), thalamus (tremor), and epileptic foci (intractable seizures) is also an important clinical application of this technology.[102] Numerous studies have demonstrated radiosurgery to be an important treatment option for many otolaryngologic conditions, such as skull base and neck tumors.[103–106] As the scientific understanding and clinical practice of radiosurgery develops, such technology may become an increasingly valuable, minimally invasive option for treating a range of pediatric general surgical diseases.

Stereotactic radiosurgery 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 of a desired tissue area. To achieve this, the patient's anatomy must usually be fixed using a stereotactic frame.[96] 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, to the treatment room. Radiosurgical treatment is then delivered to the appropriate tissue using this coordinate system.

Stereotactic Radiosurgical Platforms

Currently, there are several classes of stereotactic radiosurgery systems in use. These include heavy-particle radiosurgery systems, Gamma Knife radiosurgery, and linear accelerator radiosurgery. Currently, heavy particle radiosurgery systems and Gamma Knife radiosurgery systems are only used to treat intracranial lesions. In contrast, linear accelerator systems have been adapted to treat both cranial and extracranial lesions.

Linear Accelerator Radiosurgery

Linear accelerators, or linacs, have long been a mainstay of standard fractionated radiotherapy and were modified for radiosurgery in 1982.[96] Linac radiosurgery has 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 the surrounding normal tissue.[96] 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 6 times more active centers than Gamma Knife facilities.[96]

Frameless Image-Guided Radiosurgery

Recently, novel systems have been developed that use linear accelerators with innovative hardware and software systems capable of performing frameless image-guided radiosurgery. One such system, the CyberKnife (Accuray, Sunnyvale, Calif.), uses a lightweight linac unit, designed for radiosurgery, mounted on a highly maneuverable robotic arm.[107] The robotic arm can position and point the linear accelerator with 6 degrees of freedom and 0.3-mm precision. In addition, the CyberKnife system features image guidance, which eliminates the need to use skeletal fixation.[102,108] The CyberKnife acquires a series of stereoscopic radiographs that identify a preoperatively placed gold fiducial. This fiducial is placed under local anesthetic 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 patient's target anatomy in near real-time during treatment.[102,108] With this image guidance system, the CyberKnife is able to function without a fixed stereotactic frame, enabling fractionation (often termed hypofractionated radiosurgery or radiotherapy) of treatments as well as extracorporeal stereotactic radiosurgery. In pediatric surgery, this may represent a significant technical advantage, because it may enable the use of radiosurgery for the treatment of intrathoracic and intraabdominal pathologies (Fig. 4-11). Similarly, the Novalis Tx (Varian Medical Systems, Palo Alto, Calif.) uses an integrated cone beam CT scan system to provide volumetric imaging as well as fluoroscopic imaging to compensate for respiratory motion to enable frameless, image-guided radiosurgery. In contrast, the Trilogy system (Varian Medical Systems, Palo Alto, Calif.) uses real-time optical guidance to direct radiation delivery to the target lesion (Fig. 4-12). Both of these systems use a multileaf collimator that adapts radiation treatment to complex shapes. In addition, they use intensity modulation to help limit toxicity to surrounding tissue. Both systems deliver treatments in sessions of less than 30 minutes, which may decrease the need for sedation in pediatric patients.[109] Furthermore, the Trilogy system minimizes radiation exposure further by using an optically based guidance system.[109]

FIGURE 4-11 Cyberknife System (Courtesy Accuray, Sunnyvale, Calif.) *(See Expert Consult site for color version.)*

FIGURE 4-12 Trilogy Radiosurgery System (Courtesy Varian Medical Systems, Palo Alto, Calif.) *(See Expert Consult site for color version.)*

CLINICAL APPLICATION OF STEREOTACTIC RADIOSURGERY IN CHILDREN

To date, pediatric radiosurgery has primarily been used to treat intracranial pathologies. Hadjipanavis and colleagues reported a series of 37 patients (mean age 14) with unresectable pylocytic astrocytomas treated with stereotactic radiosurgery.[110] They found radiosurgery to be a valuable adjunctive strategy in patients whose disease was not amenable to surgical therapy.[110] Somaza and colleagues reported their experience with the use of stereotactic radiosurgery for the treatment of growing and unresectable deep-seated pilocytic astrocytomas in 9 pediatric patients.[111] Two of the patients had already failed fractionated radiotherapy, and 7 patients were considered to be at high risk for adverse radiation effects given their young age. After 19 months follow-up, there was a marked decrease in tumor size in 5 patients, while the remaining 4 patients displayed no further tumor growth. Overall, the authors felt that stereotactic radiosurgery offered a safe and effective therapy in the management of children with deep, small-volume pilocytic astrocytomas.[111]

The use of stereotactic radiosurgery for the treatment of nonmalignant intracranial lesions in children has also been described. Specifically, the use of radiosurgery for the treatment of cerebral arteriovenous malformations (AVMs) has been reported. Although microsurgical resection remains the treatment of choice for most accessible AVMs, lesions located in critical cortical areas or in deep portions of the brain are increasingly treated with radiosurgery because of the risk of surgical resection.[112] Foy and colleagues reported a series of 60 pediatric patients with AVMs treated with radiosurgery. Nidus obliteration was reported at 52% after a single radiosurgery session, increasing to 63% with repeated sessions.[112] Similarly Nicolato and colleagues reported a cohort of 62 children with AVMs treated with radiosurgery. They reported an obliteration rate of 85.5%.[113] Overall, these authors conclude that stereotactic radiosurgery is a safe and effective option for properly selected children with AVMs. In particular, it may benefit children with AVMs located in critical portions of the brain where surgical resection may pose a large risk.[112]

Compared with the adult population, the experience with stereotactic radiosurgery in children is still limited. The early reports described above all highlight the safety and efficacy of radiosurgery as a treatment modality, but clinical follow-up is still early, with many of the reports limiting the use of radiosurgery to the treatment of surgically unresectable disease. Despite relatively limited experience, the use of stereotactic radiosurgery in children may offer several theoretical advantages specific to the pediatric population. Compared with standard, fractionated radiotherapy, stereotactic radiosurgical techniques deliver conformal radiation treatment with millimeter versus centimeter accuracy. All radiation treatments are a balance between providing enough radiation to effectively treat pathologic tissues while minimizing harmful exposure to adjacent normal tissues. In pediatric patients, the distances between normal and pathologic tissues may be very small. In addition, the developing brains of children may be more sensitive to the effects of ionizing radiation than adult brains. In particular, potential cognitive and endocrine disabilities have been described in children after radiotherapy to the brain.[111,114,115] 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 use only one or few treatment sessions. As detailed above, standard, fractionated radiotherapy often uses tens of treatment sessions to maximize the beneficial effects of the treatment while minimizing the harmful effects to normal tissues. In children, these multiple treatment sessions may represent a significant challenge. In smaller children, sedation, or even 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 the child.

Although the advantages of stereotactic radiosurgery in the pediatric population appear promising, it should be noted that there also exist 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 using pins and screws. In adults, this can often be performed using only local anesthetic agents. In children, this likely requires significant sedation and possibly general anesthesia. Furthermore, the skulls of infants are soft and less rigid, because their cranial sutures have not yet fused. Because of this, standard stereotactic frames often cannot be applied. Similarly, radiosurgery treatment sessions require the patient to remain still in order for the systems to accurately deliver the radiation treatment. Adults are able to cooperate with the therapy and do not require sedation, whereas younger children and infants may require conscious sedation or general anesthesia. Although this drawback is limited by the relatively few sessions necessary with radiosurgery, it still diminishes the minimally invasive nature of the therapy compared with its application in the adults.

Recently, frameless, image-guided stereotactic radiosurgery has been reported in children. Giller and colleagues described the use of the CyberKnife system in 21 patients, ages ranging from 8 months to 16 years, with tumors considered unresectable. Diagnoses included pilocytic astrocytomas, anaplastic astrocytomas, ependymomas, medulloblastomas, atypical teratoid/rhabdoid tumors, and craniopharyngiomas. Local control was achieved in the patients with pilocytic and anaplastic astrocytoma, three of the patients with medulloblastoma, and the three with craniopharyngioma, but not for those with ependymoma. There were no procedure-related mortalities or complications, and local control was achieved in more than half of the patients. Seventy-one percent of patients received only one treatment session, and 38% of patients did not require general anesthesia. No patients required rigid skull fixation.[115] In an additional report, the same group highlighted the use of the CyberKnife system to perform radiosurgery in five infants.[114] 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."[114]

Whereas the use of stereotactic radiosurgery for intracranial lesions is well established, its use for treatment of extracranial lesions, specifically intrathoracic and intraabdominal pathologies is still developing. Intracranial contents can be easily immobilized using stereotactic frames, while abdominal and thoracic organs show significant movement resulting from respiration, peristalsis, and so on. As a result, only a small body of literature exists regarding the application of stereotactic radiosurgery for extracranial lesions. Recently, several reports have described the efficacy of stereotactic radiosurgery in adults for the treatment of lesions in the liver,[117,118] pancreas,[119,120] lung,[118,121] and kidney[122,123] —anatomical areas that have traditionally been under the watch of general surgeons. Novel image guidance technologies as well as soft tissue immobilization devices are used to make these therapies possible.

At this time, the majority of the literature represents 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 of these reports have focused on the adult patient population with no significant reports in children. Despite this inexperience, the technology surrounding stereotactic radiosurgery is rapidly developing and shows significant promise toward the minimally invasive treatment of potentially poorly accessible lesions. Newer, frameless, image-guided systems may some day 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, thus allowing gamma probe detection.[124–126] For the most part, nonspecific binding and systemic persistence has minimized the signal-to-noise ratio, thus limiting this approach. The Food and Drug Administration (FDA) approved several new radiolabeled antibodies for the identification of occult metastases in patients. Beyond imaging, the theoretical opportunity to use a gamma probe to identify "hot spots" adds a new source of information to the surgeon. Full exploitation of this methodology beyond specific functioning endocrine tumors and draining nodal basins in breast cancer and melanoma shows real promise.

NEXT-GENERATION MINIMAL ACCESS SURGERY

Minimal access surgery (MAS) forms the cornerstone of clinical innovation in present day pediatric surgery. Most pediatric general surgical procedures are now performed using some minimal access approach, and in many cases, these approaches are now considered standard of care. The next evolution in pediatric MAS involves further implementation of laparoscopic, endoscopic, and imaging techniques, with the ultimate goal of achieving scarless and painless surgery. Termed *stealth surgery,* this is an emerging surgical paradigm that encompasses a variety of techniques, each with the goal of performing complex operations without leaving visible evidence that they occurred.[127] This is achieved by placing incisions in inconspicuous or camouflaged locations and using MAS technologies to perform the operation. Examples of stealth surgery include subcutaneous endoscopy, single-incision laparoscopy, and natural orifice translumenal surgery (NOTES).

Traditionally, surgical culture has discounted the importance of scarring caused by surgical procedures. Scarring has been seen as either an unfortunate necessity or a minor outcome issue. This is interesting considering that the surgical scar is often the only collateral outcome of an operation that lasts a lifetime. At best, incisions have been placed in skin creases in an effort to camouflage the scar. Despite this, scarring is unpredictable, particularly if the scar is hypertrophic, keloid, or stretched, or if it becomes infected. There is evidence to suggest that visible scarring in children can result in reduced self-esteem, impaired socialization skills, and lower self-ratings of problem-solving ability.[128,129] Furthermore, other children judge children with facial deformities more negatively than those without facial deformities. Scarring of the chest and abdominal wall has not been as extensively studied, but it is likely that, at least in some circumstances, it can also have psychological implications. Stealth surgery aims to address surgical scarring, and collectively reflects a greater responsibility of surgeons toward the collateral damage of surgical procedures.

Subcutaneous Endoscopy

Subcutaneous endoscopy involves tunneling under the skin from inconspicuous locations to target removal of lesions at more conspicuous locations. Many surgical subspecialties, including plastic surgery,[130] otolaryngology,[131] and maxillofacial surgery,[132] have used subcutaneous endoscopic techniques, typically through hidden incisions on the scalp, for management of a variety of benign forehead lesions. Endoscopic removal of such lesions through scalp incisions using browlift equipment is also described in the pediatric general surgery literature,[133] as is removal of neck lesions through two or three small incisions placed in the axilla. This latter approach, called transaxillary subcutaneous endoscopy, has been used to address torticollis,[134] and also to remove lesions, such as

thyroglossal cysts, cervical lymph nodes, parathyroid adenomas,[135] and thyroid nodules.[136] Transaxillary access has also been used for subcutaneous lesions of the chest wall, such as dermoid cysts and lipomas.[137]

Subcutaneous endoscopy for forehead lesions is performed through a 1.5- to 2.0-cm scalp incision using standard browlift equipment (Fig. 4-13). Dissecting instruments of 2- to 3-mm diameter are passed inline through the same incision as the endoscope. The subperiosteal plane is most commonly used to approach the lesion, but the subgaleal plane can also be used. The approach is ideal for lateral brow dermoid cysts or those found between the eyebrows (nasoglabellar cyst). The approach is not used for lesions that have intracranial extension.

Transaxillary subcutaneous endoscopic excision of neck lesions is performed by placing two or three endoscopic ports in the ipsilateral axilla, posterior to the lateral border of the pectoralis major muscle (Fig. 4-14). A subcutaneous workspace is then created, extending to the neck. The platysma muscle is traversed superior to the clavicle, and the target lesion is then dissected free. Recognition of landmarks and accurate anatomical orientation is subject to a learning curve, but visualization of all structures, including recurrent laryngeal nerves, is excellent. It is important to avoid extensive use of thermal energy sources in the neck, especially monopolar cautery, because of the thermal spread of such instruments. It is preferable to use bipolar cautery when possible, or else a thermal sealing/cutting device such as the Ligasure (Valleylab, Boulder, Colo.). The cosmetic benefits of this approach are apparent, because the patient is left with no scar on the face or neck. Pain is controlled with non-narcotic analgesics, and patients can typically be discharged the same day.

Single Incision Laparoscopy

Single incision laparoscopy is an evolution of minimal access surgery that promises virtually scarless abdominal operations. Various acronyms, including SILS (single-incision laparoscopic surgery; Covidien), LESS (laparoendoscopic single-site surgery), SPA (single-port access surgery),[138] OPUS (one-port umbilical surgery), and SAS (single-access site surgery) have been applied to this technique. The essential element is the use of a single small incision, usually placed at the umbilicus through which multiple laparoscopic instruments are passed either through a single-port device with multiple conduits or through multiple closely spaced ports (Fig. 4-15). Single incision approaches have been described in the adult literature for appendectomy, nephrectomy,[139] adrenalectomy,[140] cholecystectomy,[141] and colectomy,[142] and in the pediatric general surgical literature for appendectomy,[143] varicocelectomy,[144] cholecystectomy, and splenectomy.[145]

Cosmesis is the most apparent benefit of single-incision laparoscopy, because the single scar produced can be effectively hidden in the existing umbilical scar. The cosmetic benefit, including psychosocial factors, has not been objectively demonstrated, but the complete absence of a visible scar is achievable with this method. The procedures are feasible in equivalent operative times to standard laparoscopy,

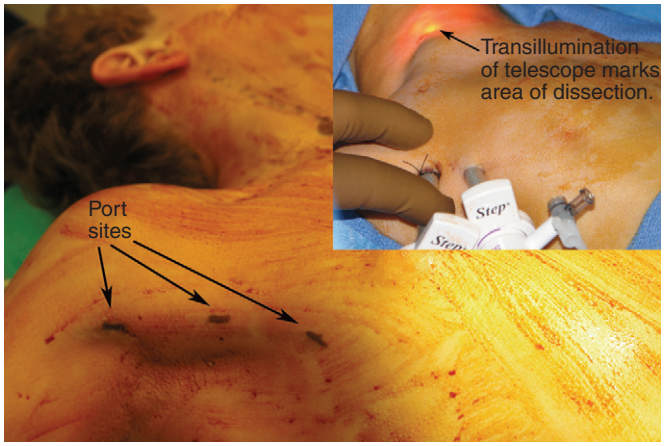


FIGURE 4-14 Transaxillary subcutaneous access can be used to access lesions in the neck and chest wall. A cavernous subcutaneous workspace is created to facilitate dissection. In this image, the light at the tip of the telescope can be seen transilluminating the skin. *(See Expert Consult site for color version.)*

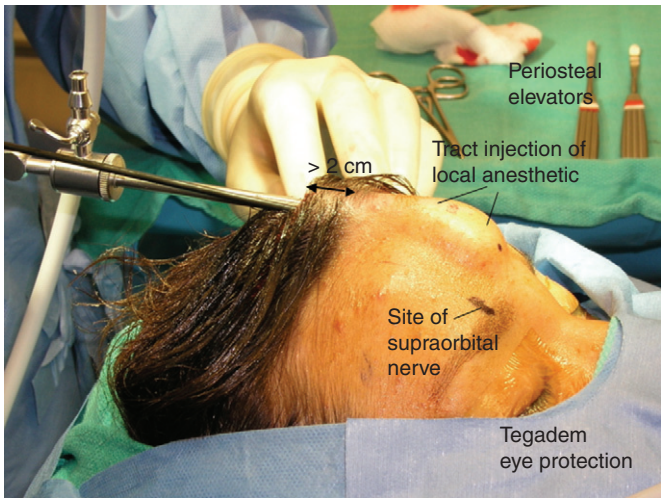


FIGURE 4-13 For endoscopic excision of forehead lesions, hydrodissection with local anesthetic is used to create a path toward the lesion in the subperiosteal or subgaleal plane, starting about 2 centimeters posterior to the hairline. The telescope and dissecting instruments are placed through a 1 to 2 cm V-shaped incision on the scalp. *(See Expert Consult site for color version.)*

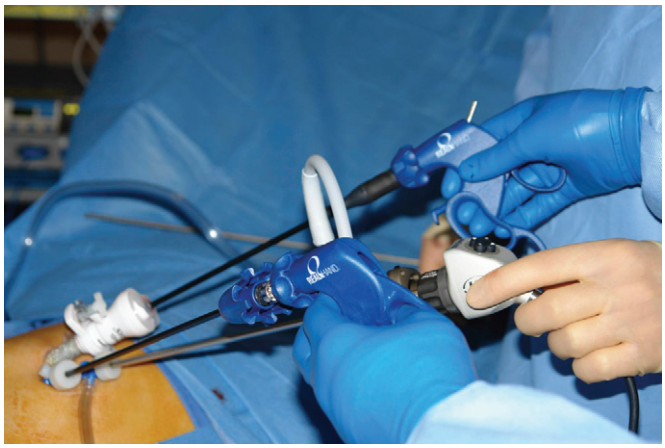


FIGURE 4-15 Single-incision laparoscopic surgery involves placing multiple ports, or a commercially available single-port device, at the umbilicus. Instruments with dexterous end effectors can be exploited to achieve triangulation around the target tissue, which is otherwise difficult to achieve with standard rigid laparoscopic instruments in this setting. *(See Expert Consult site for color version.)*

without additional safety concerns. Although clinical trials are underway, outcomes in terms of pain, recovery, and hospital stay have not been assessed—anecdotally these outcomes mirror those of standard laparoscopy.

A number of critical challenges in performing single-incision laparoscopy have led to some innovative solutions. (1) Close co-location of the instruments can result in bothersome instrument backend, hand, and camera collisions that impair mobility. This is addressed with the use of ports and instruments of varying lengths to offset backends, angled light-cord adapters for rigid telescopes, or flexible tip telescopes with low-profile backends. (2) When using standard rigid laparoscopic instruments, it is difficult or impossible to achieve an equal degree of triangulation around the target tissues (ideally 60 degrees) as can be achieved in standard laparoscopy and that is necessary for safe, precise, and efficient dissection. Instruments with an additional joint near their tip that gives two additional degrees of freedom (Realhand, Novare Surgical, Cupertino, Calif.; Autonomy Laparo-Angle, Cambridge Endo, Framingham, Mass.; Roticulator, Covidien, Norwalk, Conn.) have been applied to single-incision laparoscopy for this reason. With these "dexterous" instruments, triangulation can be achieved by first crossing the instrument shafts at or just below the level of the fascia, then deflecting the tips inward to create triangulation. (3) The maneuvers necessary to work with instruments in this configuration can be confusing and counterintuitive, because the instrument tips are frequently opposite the hand configuration, or the surgeon's hands are sometimes crossed. Developers of surgical telemanipulation platforms have taken advantage of computer algorithms used in their existing telemanipulation platforms (e.g., da Vinci Si, Intuitive Surgical, Sunnyvale, Calif.) to provide a single-incision laparoscopy platform that can correct for paradoxical movements and give the surgeon the perception that their hand movements are being mirrored by the robotic instruments.[146]

Single-incision laparoscopy will likely play a role in pediatric surgical procedures for larger children and adolescents, primarily because of the avoidance of visible scarring. Its role in neonatal surgery is less clear. Existing instrumentation is too large for neonatal anatomy. Furthermore, proponents of umbilical laparotomy show that most abdominal procedures can be performed in neonates through umbilical incisions that can be camouflaged with an umbilicoplasty.[147] When possible, this approach offers a cheaper alternative to single-incision laparoscopy. Cost continues to be a consideration when adopting these novel minimal access procedures, because they generate the need for more complex technologies, but a cost assessment is difficult to perform in the early stages of adoption because of the dynamic nature of the technologies used and the costs they incur.

NATURAL ORIFICE TRANSLUMENAL ENDOSURGERY

Perhaps a more extreme evolution of scarless surgery is natural orifice translumenal endosurgery (NOTES), which aims to perform abdominal or thoracic procedures by way of transoral, transgastric/transesophageal, transrectal or transvaginal access. Some surgeons consider single-incision laparoscopy a bridge to NOTES, while others see at as a more palatable alternative to NOTES. In adults, the potential advantages of NOTES include decreased or no postoperative pain, no requirement of general anesthetic, the performance of procedures in an outpatient setting, and possibility of reducing costs. In children, NOTES remains uncharted, and its application in this population seems not only conceptually unappealing (transvaginal access is unlikely to be considered in a young girl), but also currently fraught with undue risk (leakage and infection risk with transgastric or transrectal access). Adult subjects asked to rate their preference of technique in the absence of safety profile data preferred single-incision laparoscopy and standard laparoscopy versus NOTES and open surgery.[148] However, there are unique pediatric surgical conditions described below that are intriguing targets for this approach, and research in this area allows an opportunity to discover novel techniques and technologies that may be more generally applicable to pediatric minimal access surgery.

The development of NOTES is an interesting case study in surgical innovation because of the way it has progressed, in contrast to conventional laparoscopy. The rapid adoption of laparoscopy into mainstream surgical practice without oversight or appropriate training heralded increased complication rates, such as that of bile duct injury during laparoscopic cholecystectomy[149] and complications not previously seen, such as intestinal and vascular injury from port placement. To avoid a similar scenario with NOTES, delegates from the American Society of Gastrointestinal Endoscopy (ASGE) and the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) established the Natural Orifice Surgery Consortium for Assessment and Research (NOSCAR),[150] with the purpose of defining guidelines for the safe, ethical, and evidence-based development of NOTES. The technical challenges, and hence areas of research focus, they identified included (1) creation and secure closure of the defect created in the hollow viscus for peritoneal access, (2) prevention of peritoneal contamination and maintenance of sterility, (3) adequate visualization and orientation in the peritoneal cavity, and (4) effective instrument triangulation around target tissues and adequate retraction of adjacent tissues.

A second unique feature of NOTES is the early involvement of industry in device development, in close collaboration with both surgeons and gastroenterologists with an interest in therapeutic endoscopy. Both specialties have recognized the need to collaborate on NOTES development because of its hybrid use of endoscopic and laparoscopic techniques. The medical device industry, in turn, has engaged early in this effort to remain competitive and obtain market share in this potentially large market. Although widespread use of NOTES has not materialized, research and development in this area has resulted in the development of a host of novel technologies ranging from dexterous flexible endoscopic surgical tools to intraluminal suturing devices.

In pediatric surgery, the adoption of NOTES for common pediatric conditions in the near future seems improbable because of small markets, the persistent need for general anesthetic, and a lack of any clear significant benefit versus single-incision laparoscopy. There are, however, some interesting possibilities for the use of NOTES in neonatal surgery, such as for duodenal atresia, urologic anomalies, and esophageal atresia. The latter is perhaps the most compelling. Although a thoracoscopic approach to esophageal atresia is well described, there has been slow adoption of this approach because of its technical difficulty, particularly with respect to

thoracoscopic suturing of the anastomosis, which requires very precise movements in a limited workspace with highly fragile tissues that are under tension. The possibility of performing some or all of the operation transorally using flexible tools with purpose-specific attachments that allow fistula closure and/or esophageal anastomosis may allow a wider adoption of a minimal access approach to this condition by trivializing the technical difficulty of creating the anastomosis. Unfortunately, market sizes for diseases such as esophageal atresia do not support investment in purpose-specific technology, but development of dual-purpose tools that can also be applied to larger (adult) markets may provide the basis for their development.

Endolumenal Therapies

Innovations in intraluminal endoscopic therapies have centered mainly on totally endoscopic antireflux procedures, some of which have been applied to children. Some of these procedures (Enteryx, Gatekeeper) have fallen out of favor because of safety concerns or lack of efficacy. Use of Enteryx came to a halt in 2005 when the FDA requested a recall by Boston Scientific of all Enteryx systems following reports of adverse effects (and cases of fatality) resulting from inadvertent Enteryx injection into the mediastinum, pleural space, and aorta (with consequent arterial embolism). The Enteryx system is mentioned here only to exemplify the potential for serious complications with novel technologies, and reinforce the need for proper efficacy and safety trials before their widespread application, particularly in the pediatric population.

Use of other devices, such as Endocinch (Bard, Warwick, RI), Stretta (Curon Medical, Sunnyvale, Calif.), NDO Plicator (NDO Surgical, Mansfield, Mass.), have shown short-term improvements in gastroesophageal reflux disease (GERD) symptoms but without objective evidence of reduced lower esophageal acid exposure or long-term durability.[151] The Stretta procedure was the first interventional endoscopic GERD therapy to gain FDA approval in 2000. Consisting of a catheter, soft guidewire tip, balloon basket assembly, and four electrode delivery sheaths positioned radially, the Stretta device uses radiofrequency (RF) energy to increase the tone of the lower esophageal sphincter (LES). Its mechanism of action is unclear, but it is believed that the RF energy results in shrinkage of collagen fibers, resulting in elevation of postprandial LES pressure[152] and reduction of transient lower esophageal sphincter relaxations. Islam and colleagues studied the effects of the Stretta procedure on a small series of six pediatric patients (mean age 12 +/− 4 years), concluding that the procedure was safe and effective.[153] Five of the six patients were asymptomatic at 3 months, and three were able to discontinue antisecretory medication. Mean reflux score improved significantly after 6 months; however, pH studies were not done. Without significant improvements in acid exposure, the benefit of this procedure in children is questionable, because common indications for surgical management of pediatric GERD consist mainly of complications of esophageal acid exposure, such as esophagitis, pharyngitis, or aspiration, as opposed to minor GERD symptoms.

Also approved for use by the FDA in 2000, the EndoCinch system aims to reduce gastric reflux by pleating the gastroesophageal junction (GEJ). The 30- to 60-minute procedure begins with insertion of the Endocinch device through an overtube. Suction applied 1 to 2 cm below the squamocolumnar junction facilitates full-thickness placement of two adjacent sutures. The sutures are then "cinched" together or brought into approximation, to create a pleat. Usually several pleats are created, significantly narrowing the lumen at the GEJ. The resulting rosette of tissue (gastroplication) is intended to prevent reflux of gastric contents into the esophagus. Only one pediatric study describes the effects of the Endocinch system for treating GERD.[154] Seventeen patients with median age 12.4 years (range, 6.1 to 15.9 years) underwent gastroplication. All patients showed significant improvement in early postoperative assessments of symptom severity, symptom frequency, and quality of life. These effects persisted at 1-year follow-up in the majority of patients and were reflected in reduced pH indices. In adult patients, lack of long-term durability has been attributed to suture degradation and loss, both demonstrated on follow-up endoscopy.[155,156] The reason for the longer durability of this procedure in children compared with adults is unclear but may be a consequence of a greater ability to achieve full-thickness esophageal bites in the smaller patients.

The latest transoral endoscopic device on the market is the EsophyX (Endogastric Solutions, Redmond, Wash.), which is designed to achieve transoral incisionless fundoplication (TIF). The goal of this antireflux procedure is to endoluminally create an anteriorly placed 3- to 5-cm, 200- to 270-degree valve at the distal esophagus secured by special fasteners. The end result is creation of an antireflux barrier and reestablishment of the angle of His. The device does not have to be inserted and removed for each stitch, and its function allows reduction of a small hiatal hernia, although the crura remains unapproximated. Although adult studies have shown long-term reductions in proton pump inhibitor use, improved quality of life, and reduced esophageal acid exposure, data for the pediatric population is forthcoming.[157] Use of the device is limited only to larger children whose esophagi can accommodate a device that is 18 mm in diameter.

SURGICAL ROBOTICS

Innovations in endoscopic technique and equipment continue to broaden the range of applications in minimal access surgery. However, many minimal access 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. These difficulties are further compounded by the need to operate from a 2D video image. Robotic surgical systems have evolved to 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 complex minimal access surgical (MAS) procedures. In children, early reports described the feasibility of using surgical robots to complete common and relatively simple pediatric general surgical procedures.[158–160] More recently, the use of robotic surgical systems in human patients has been described in multiple surgical disciplines, including pediatric general surgery, pediatric urology, and pediatric cardiothoracic surgery.[161–163] In addition, the feasibility of complex, technically challenging procedures, such as robotic-assisted fetal surgery, has been reported in animal models.[164,165]

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.[166] 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. Under this classification, there are currently three types of robots 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 (Curexo Technology, Fremont, Calif.) that is used in orthopedic surgery to accurately mill out the femoral canal for hip implants.[167] Another example is the CyberKnife system, previously referenced, which consists of a linac mounted on a robotic arm to precisely deliver radiotherapy to intracranial and spinal tumors.[168,169]

The second class of robot is the surgical-assist devices, where the surgeon and robot share control. The most well-known example of this group is the AESOP (*A*utomatic *E*ndoscopic *S*ystem for *O*ptimal *P*ositioning; formerly produced by Computer Motion, Goleta, Calif.). This system allows a surgeon to attach an endoscope to a robotic arm that 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.

The final class consists of robots whose every function is explicitly controlled by the surgeon. The hand motions of the surgeon at a control console are tracked by the electronic controller and then relayed to the slave robot in such a manner 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 robotic-assisted surgery have involved this 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	da Vinci System

Current Status of Robotic Technology Used in Pediatric Surgery

Currently, there is only one commercially available robotic surgical system—the da Vinci Surgical System (Intuitive Surgical, Sunnyvale, Calif.). Though the da Vinci is popularly referred to as a surgical robot, this is a misnomer, because "robot" implies autonomous movement. The da Vinci does not operate without the immediate control of a surgeon. A better term may be "computer-enhanced telemanipulators." However, for the sake of consistency with published literature, this chapter will continue to refer to such systems as robots.

The da Vinci Surgical System The da Vinci system is made up of two major components (Figs. 4-16 and 4-17).[162] 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.

The operative surgeon is seated at the surgeon's console, which can be located up to 10 meters 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 finger tips. 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 that uses two medical-grade cathode ray tube (CRT) monitors to display a separate image to each of the surgeon's eyes.

The standard da Vinci instrument platform consists of an array of 8.5-mm diameter instruments. These instruments provide 7 degrees of freedom through a cable-driven system.

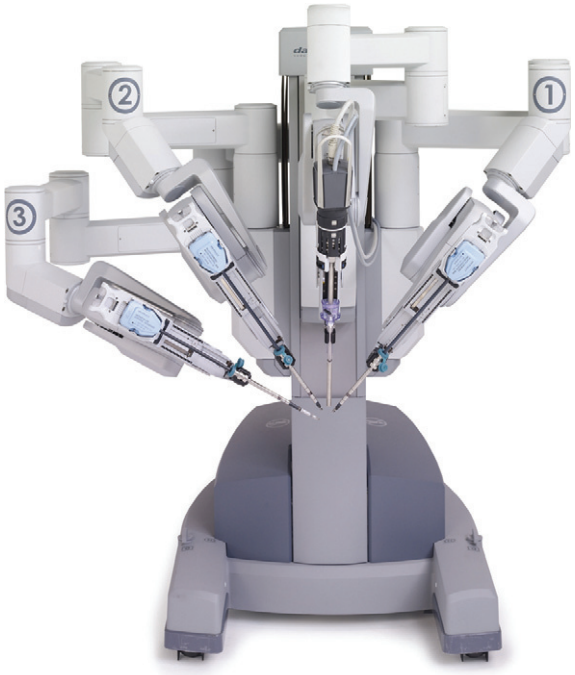


FIGURE 4-16 The Intuitive Surgical da Vinci Si robotic surgical system (Courtesy Intuitive Surgical, Sunnyvale, Calif.) *(See Expert Consult site for color version.)*

FIGURE 4-17 The Intuitive Surgical da Vinci Si robotic surgical system. (Courtesy Intuitive Surgical, Sunnyvale, Calif.) *(See Expert Consult site for color version.)*

A set of 5-mm instruments are also available. These instruments use a "snake wrist" design and also provide 7 degrees of freedom (Fig. 4-18).

Since its inception in 1995, the da Vinci system has undergone several iterations. The current system, called the da Vinci Si, features high-definition optics and display as well as smaller and more maneuverable robotic arms. Other features include dual console capability for training purposes.

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 the 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, the 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 the novice laparoscopist.

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.[170,171] This enhanced visualization is taken a step further with robotic systems, because they are capable of providing a highly magnified, 3D image. The 3D vision system adds an additional measure of accuracy by enhancing depth perception and magnifying images by a factor of ten. The alignment of the visual

FIGURE 4-18 Articulated robotic instrument. (Courtesy Intuitive Surgical, Sunnyvale, Calif.) *(See Expert Consult site for color version.)*

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. The system also allows for variable motion scaling from the surgeon's hand to the instrument tips. For instance, a 3:1 scale factor maps 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 and more precise.[160]

The da Vinci system uses instruments that are engineered with articulations at the distal end that increase their dexterity compared with 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. The da Vinci instruments feature 7 degrees of freedom (including grip), while standard laparoscopic instruments are only capable of 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 bariatric patients.

Although robotic surgical systems provide several key advantages versus standard minimal access surgery, there are a number of technological limitations specific to pediatric surgery. First and foremost is the size of the robotic system. Compared with many pediatric surgical patients, the size of the da Vinci surgical cart 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.[170]

The size and variety of available robotic instruments is limited compared with those offered for standard laparoscopy. Currently, the da Vinci system is the only platform undergoing further development at the industry level. A 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 compared with the original 8.5-mm instruments regarding diameter, the number of instruments offered is still somewhat limited. Furthermore, these instruments use a new "snakewrist" architecture that requires a slightly larger amount of 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.

There are a number of general limitations inherent to the available robotic surgical system that must be overcome before they are universally accepted in pediatric as well as adult surgery. These include the high initial cost of the robotic systems as well as the relatively high recurring costs of the instruments and maintenance.[162] In addition, this system does not offer true haptic feedback.[170] Even though such feedback is reduced in standard minimal access surgery compared with open surgery, it is further reduced or absent with a robotic interface. This disadvantage is partially compensated for by the improved visualization offered by the robotic systems, but it remains a potential drawback when precise surgical dissection is required.

The robotic systems require additional, specialized training for the entire operating room team. This translates into robotic procedure times that are predictably longer when compared with the conventional laparoscopic approach, at least until the surgical team becomes facile with the 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 robotic-assisted case.[170]

Applications of Robotic Technology to 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 robotic-assisted surgery. A wide variety of abdominal and thoracic procedures have been reported in the fields of pediatric general, cardiothoracic, and urologic surgery. The bulk of the literature represents class IV evidence, consisting of case reports and case series with no class I evidence. In 2009, van Haasteren and colleagues[172] reviewed the literature and found a total of eight peer-reviewed case series and five studies comparing robotic surgery with open or conventional laparoscopic surgery. Several of the studies had a retrospective design, and there were no randomized studies. From their review, they concluded that the published literature demonstrates that robotic surgical systems can be safely used to perform a variety of abdominal and thoracic operations. They were not able to identify evidence that robotic-assisted surgery provided any improvement in clinical outcomes compared with conventional open or laparoscopic surgery.[172]

The first reports describing the use of robotic surgical systems for abdominal procedures in children were published in 2002,[158,160] and robotic-assisted surgery has only seen modest adoption in the field of pediatric general surgery. The cause of this is likely multifactorial and in many ways mirrors the adoption curve seen in adult general surgery. To date, robotic-assisted surgery has found the most widespread adoption in the field of adult urology, specifically for prostatectomies. This operation takes advantage of the strengths of the current robot, namely articulated instruments and 3D visualization that assist in the complex dissection and reconstruction required in a narrow space. It is also a single quadrant operation that does not require significant repositioning of either the patient or the robotic system once the procedure begins. Lastly, prostatectomies are a relatively high-volume operation that is reproducible. This leads to improved efficiency, because the operating room team has only one setup to master. In contrast, the field of pediatric general surgery is characterized by a wide variety of complex but low-volume operations performed in small children. There is no high-volume operation in pediatric general surgery that takes advantage of robotic assistance. In addition, the instrument size and haptic limitations of the current robotic system are not ideal for use in many of our smaller patients.[173] These issues will likely be addressed by further advancement of the technology, with evolved incarnations of robotic surgery possibly playing a larger role in pediatric general surgery in the future.

Microtechnologies and Nanotechnologies—Size Matters

An arsenal of technology will emerge from material science and its application principles to microelectromechanical systems (MEMS)[174,175] and nanoelectromechanical systems (NEMS). Just as the electronics industry was transformed by the ability to manipulate electronic properties of silicon, the manipulation of biomaterials at a similar scale is now possible. For the last 40 years the common materials of stainless steel, polypropylene, polyester, and polytetrafluroethylene 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 and distinction in device manufacturing is that of the "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 of 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.

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 the standard integrated circuit, which includes crystal growth, patterning, and etching.[176]

MEMS devices have a particular usefulness in biologic applications because of their small volumes, low energy, and nominal forces.[177] Increased efficacy of instruments and new areas of application are also emerging from specific and successful biomedical applications of MEMS.[178] 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 can derive their own energy from an input signal, whereas passive sensors require an outside energy source to function. Almost all of 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, Pittsburgh, Penn.), which uses microfabricated pressure sensors that are attached to the blade of a scalpel (Fig. 4-19). 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 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 plaques 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 gases. 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 spectrums 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 because of the relatively small sample size, the test can be performed in less time than 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.

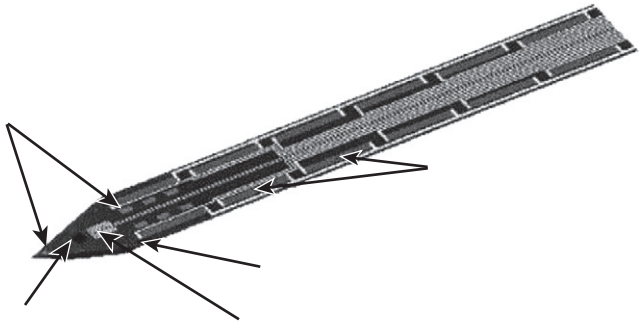


FIGURE 4-19 Data Knife MEMS-based scalpel. (Courtesy of Verimetra, Pittsburgh, Penn.)

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 that 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 piezo-resistor changes output voltage with variations in pressure. Temperature compensation and calibration can be integrated in one sensor.

Other MEMS Sensors in Medicine The Wheatstone bridge piezo-resistive 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. These types of sensors are used primarily in blood pressure monitoring equipment, but their use in the medical field extends to respiratory monitors, dialysis machines, infusion pumps, and medical drilling equipment. They are also used in inflatable hospital bed mattresses to signal an alarm upon detection of a lack of motion over a significant period of time.

Actuators

An actuator is a fluid-powered or electrically powered device that supplies force and motion. There are several kinds of actuators used in MEMS devices. These include 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. 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 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. There are disadvantages of current insulin micropumps, 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, which senses glucose and insulin levels and titrates insulin delivery, would be an interesting MEMS combination of a sensor and an actuator.

Next Steps for MEMS

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 Advanced Research Projects Agency (DARPA). 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 conglomerate of semiconductors 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, lab 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, we will view MEMS devices as common surgical modalities, smart instruments, inline laboratories, surveillance devices, and perhaps for cellular or even DNA insertion.

NANOELECTROMECHANICAL SYSTEMS

Applications of nanotechnology and nanoelectromechanical systems in medicine and surgery have been recently reviewed.[175] Size does matter. In medicine and biology, the major advantage of decreasing 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 are welded or "sintered" by heat treatment on top of the bulk material.[179] This bead layer optimizes bone ingrowth, while the bulk material is responsible for the mechanical stability of the device. Hydroxyapatite-coated implants represent a biologically advanced coating of the device with ceramic hydroxyapatite,[180] thereby inducing bony ingrowth by mimicking the crystalline nature of bone (biomimicry). 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.[181] The drug coating of rapamycin or paclitaxel diffuses slowly into the tissue microenvironment to prevent a fibrotic reaction. The future ideal stent will likely be engineered to optimize the bulk material and the coating. Indeed, the perfectly biocompatible material may be one in which a bulk material is artificial and the surface is seeded with the patient's own cells, for example, an endothelialized Goretex vascular stent.[182]

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.[183] Thus NEMS processing starts with a nonsolid phase, typically a solution, and by manipulating the environment, materials are created.

Recently, biologic molecules such as proteins and DNA have been used to stabilize nanoparticle crystals and create materials with unique properties, opening the door to unlimited diversity in the next generation of nanoparticles and materials.[184,185] Such processes mimic nature's ability to produce materials such as pearls, coral, and collagen.

NEMS in 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 4-20 depicts a complex nanoparticle[186] composed of an iron oxide core surrounded by silicon oxide shells. Ligands may be attached to the silicon oxide coating that may then target the iron oxide to a specific site. Such technology can be used for diagnostic purposes based on tumor permeability and therapeutic options.

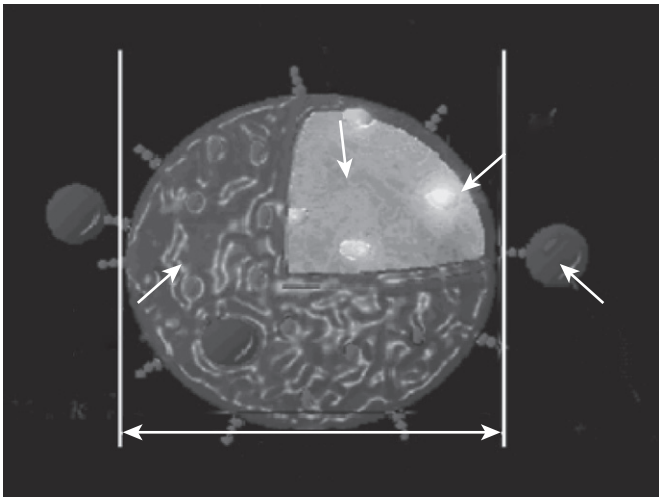


FIGURE 4-20 A schematic of a nanoparticle. An iron oxide core is surrounded by a silicon oxide shelf. Ligands attached to the silicon oxide can target the iron oxide to a specific site or potentially a tumor. The iron oxide can be heated in a magnetic field. Alternatively, the iron oxide may carry a toxin, a gene, or a pharmaceutical. Surface arrows highlight customized ligands while inner arrows point out therapeutic materials that can be placed in the iron oxide core.

Harisinghani and colleagues[186] used iron oxide nanoparticles to identify tumor metastases in lymph nodes of patients with prostate cancer. The authors demonstrated increased sensitivity and specificity in identifying nodes that ultimately contained tumor. Further work with magnetic nanoparticles functionalized with tumor-specific antibodies will enhance a specific uptake by tumors.

Surgical Innovator

Most clinical innovations in surgery relate to a novel operation, a novel device, or both. Occasionally, the novel procedure or device is of the surgeon's own development. In all cases, the surgeon holds the responsibility of ensuring that the implementation of these innovations is done in an ethical fashion. There are guidelines that surgeons can follow to help them safely and ethically introduce innovative solutions to their practice.

INNOVATIVE DEVICES

In the United States, pediatric research falls under the regulation of institutional review boards (IRBs), which serve the purpose of upholding the guidelines set forth by state and federal legislative bodies. The FDA regulates the use of all surgical devices.[187] Although the majority of pediatric surgeons will not design large clinical trials or novel devices, it is helpful to understand the regulatory processes when implementing new techniques or devices into one's practice.

The FDA categorizes new devices into three classes based on the potential risk incurred by using the device in humans. Class I devices pose minimal harm to the recipient and do not typically require premarket notification or approval (i.e., clinical data supporting safety and efficacy). Class II devices pose an intermediate level of potential harm but have demonstrated clinical efficacy comparable to similar existing devices. Class III devices pose significant potential harm to the recipient and require premarket approval with clinical data supporting safety and efficacy.

If a surgeon intends to study a novel device as part of a clinical trial in humans, the collection of preliminary data for non-FDA–approved devices is regulated by IRBs. If an IRB determines that the device provides insignificant risk to the study participants, the study may proceed. However, if an IRB concludes that the proposed study exposes the participants to significant risk, the FDA must approve an investigational device exemption prior to commencement of the study.[187]

If a device treats a condition that affects less than 4000 people per year in the United States, which applies to most pediatric conditions, it may qualify for humanitarian device exemptions (HDE). This allows approval of such devices when safety has been demonstrated and the probable benefits outweigh the risks of using the device.[187] HDE aids in disseminating high-impact technologies designed for rare conditions, technologies that would otherwise have delayed time to market because of the inability to properly power premarket clinical trials.

The pediatric surgeon using a novel non-FDA–approved device should obtain IRB approval. If there is sufficient patient risk associated with the use of the novel device, the investigator must obtain investigational device exemption from the FDA. Once clinical safety and efficacy are established, one can apply for FDA approval. If the device has significant potential benefit for an uncommon disease, the investigator has the option to apply for an HDE.

INNOVATIVE PROCEDURES

An innovative procedure may be composed of a new way of surgically correcting a condition, with or without the use of a device not approved for that use. Minor modifications to existing procedures would not be included in this category. The off-label use of an adult device in children may or may not be seen as innovative, depending on the circumstances surrounding its use. In all cases, a reasoned approach, such as that outlined in Table 4-3, can help to ensure safe and effective implementation of the innovation.

The Department of Health and Human Services (DHHS) categorizes pediatric research into four successive categories based on the degree of risk and the potential benefit to the study participant.[188] The first three of these codes encompass studies with potential for benefit to the participant with relatively low levels of risk exposure. The fourth code includes research that exposes participants to the potential risk in the *absence* of direct or indirect benefit but that has the potential to benefit children in general. A study that falls under this category may not be approved solely by an IRB but must have the authorization of the Secretary of the DHHS.

All pediatric research proposals, regardless of which DHHS code they fall under, must demonstrate an appropriate process for obtaining both patient *assent* and parent/guardian *consent* as defined by The American Academy of Pediatrics Committee on Bioethics.[189] The currently accepted standard of care is to obtain patient assent prior to enrollment in a study when feasible (i.e., when the patient is developmentally capable of affirming participation after receiving a cognitive age-appropriate explanation of the study/procedure, risks, benefits, and alternative options). Parental permission/consent is required whenever possible (i.e., nonemergent settings) if the patient is a nonemancipated minor. Practically speaking, parental permission/consent involves all of the components of informed consent in an adult population.

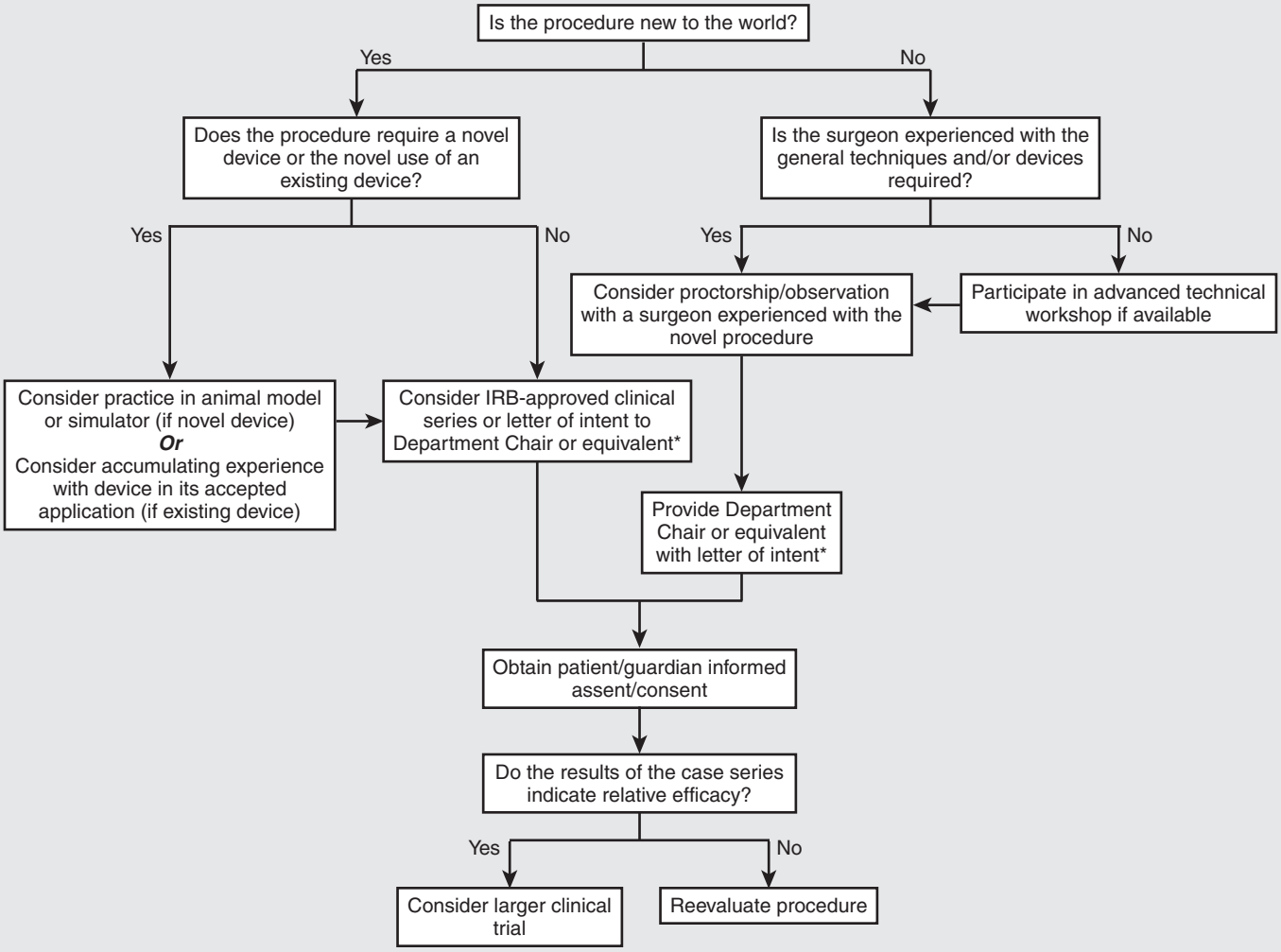
PEDIATRIC DEVICE DEVELOPMENT

The medical device industry has shown little interest in pediatric device development because of small market sizes and regulatory hurdles.[190] Similarly, entrepreneurs trying to promote medical device concepts have had little success in getting their ideas funded through typical funding channels, such as venture capital, for these same reasons. The consequence is that pediatric surgeons and others performing pediatric procedures are left to use adult devices off-label in children, "jerry-rig" their own devices, or simply do without. All of these approaches potentially result in a substandard level of care for pediatric patients.

Recognizing the dire need for pediatric-specific devices and the lack of interest from medical device companies, medical practitioners have in recent years taken a more active role in pediatric device development. More focused efforts at pediatric specific medical device innovation have emerged, in response to the dearth of innovation for this population.

TABLE 4-3

Approach to Introducing Innovative Procedures into Pediatric Surgical Practice



*Letter should include description of existing foundational technique(s), a description of the novel technique, a summary of the published results comparing the novel technique to existing technique(s) if available, and a description of the preparation undertaken by the surgeon prior to attempting the novel procedure.

From Kastenberg Z, Dutta S: Guidelines for innovation in pediatric surgery. J Laparoendosc Adv Surg Tech A 2011;21:371–374.

In September 2007, President George W. Bush signed into law the *FDA Amendments Act of 2007*, which included *Title III: Pediatric Medical Device Safety and Improvement Act*. This Act, which was designed to improve the research, manufacture, and regulatory processes for pediatric medical devices, also aimed to establish nonprofit consortia to stimulate development of pediatric devices. As a consequence, the United States Congress charged the FDA with dispersing grant funds for the creation of pediatric device consortia (PDC), organizations devoted to creating a national platform for the development of pediatric-specific medical devices, and demonstrating the timely creation of such devices. The first of these consortia include the PDC at University of California, San Francisco (http://www.pediatricdeviceconsortium.org) led by Dr. Michael Harrison, the University of Michigan PDC (http://peddev.org) led by Dr. James Geiger, the Pediatric Cardiovascular Device Consortium at Boston Children's Hospital led by Dr. Pedro Del Nido, and the Multidisciplinary Initiative for Surgical Technology Research (MISTRAL; www.mistralpediatric.org), a collaborative effort between one of the authors (SD) representing Stanford University and SRI International, an engineering firm based in Menlo Park, Calif. Notably, three of these four consortia are led by pediatric general surgeons, attesting to the pioneering role our specialty can play in the advancement of pediatric medical technologies. These consortia have taken the lead in establishing formalized collaborative ventures that engage clinical and technical expertise in needs identification, foundational science research, and device design and prototyping. Going beyond the typical role of the academic institution, these collaborative groups are also identifying paths to market for the devices they develop through such strategies as spin-off companies or partnerships with commercialization entities.

Furthermore, the consortia provide pediatric surgeons-in-training an opportunity to immerse themselves in the innovation process, focusing specifically on the unique challenges of developing devices for children.

The market strategy for pediatric devices depends on the nature of the device. For example, many pediatric applications may require a device to be miniaturized for use in children. The technical solutions used to achieve this can then be applied in much larger adult markets. In areas such as minimal access surgery, smaller devices are also seen as beneficial for adult applications. This "trickle up" effect of the technology to adult applications can justify production of the device for pediatric markets because of the potential to also use it in much larger adult markets. Licensing to commercialization entities interested in applying the technology to adult markets may come with the caveat that they also address the pediatric need. In some circumstances where the device is quite specific to a rare pediatric condition, philanthropic support may be necessary to help it get to market, such as that by an individual or a foundation with particular interest in child health or the specific disease.

Device development can be seen as a form of translational science, where the basic research, design, prototyping, and testing of novel devices comprise unique intellectual contributions. Some institutions are beginning to recognize the scholarly potential for device innovation and crediting the researchers engaged in it, thus making it a potential basis for academic promotion. The measures of scholarly productivity may be different than traditional research tracks but nevertheless hold value for the academic institution. For example, device innovators may not be able to publish extensively because of concerns about protection of intellectual property (at least in the initial stages of device development), but the generation of grants, patents, and usable devices that positively impact healthcare can have great value for the institution.

Innovative Surgical Training

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 addressed. Simulation and virtual reality (VR)[191,192] are two concepts that may reshape the way we think about surgical education, rehearsal, and practice.

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 licenses. 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 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.[193]

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, which is related to both the underlying disease and the therapeutic modality. Risk can be reduced through training. One of the ways to accomplish both of 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.[194] It is commonly assumed that the 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 experiences that evolve substantial aspects of the real world in a fully interactive manner.[195] To perform a simulation, it is only necessary to involve the user in a task or environment that is sufficiently "immersive" so 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. Just as one can simulate a National Football League football game with a console gaming system, surgeons can learn to tie knots using computer-generated virtual reality, 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 emergent 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 that are 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.[196]

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. For example, mannequin simulators, although internally complex, can serve to complement the

simulation environment. Simulation of procedures, such as laparoscopic operations, should use displays similar to those used in the actual operating room.

Simulation of open procedures, on the other hand, requires systems that are presently in the developmental stages. The level of interaction between the surgeon and the simulated patient requires an immersive visualization system, such as a head-mounted display. 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.[176] These systems involve the use of a high-resolution monitor screen at the level of the operating table. 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. Tactile feedback is the perception of a sensation applied to the skin, typically in response to contact. Both tactile and force feedback were necessary developments, because the user needs the sensation of touching the involved virtual objects. This so-called ***haptic loop***, or the human-device interface, was originally developed with remote surgical procedures in mind and has much to lend to the evolution of surgical simulation.

Technologies that can address haptic feedback are maturing, as noted by rapid development of haptic design industries in the United States, Europe, and Japan and in many university-based centers.[197] Haptic technologies are used in simulations of laparoscopic surgical procedures, but 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 3D, interactive, graphic images of a surgical field is the next level in surgical simulation. Seeing and manipulating an object in the real world is altogether 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, this 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 problem produces such drastic changes that the computer program supporting the simulation is frequently incapable of handling such complexity. This also does not include the issue of blood flow, which would cause additional changes to 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 real-time changes in the organ's architecture, which would occur after a simulated incision.

A more distinct approach to the solution for this problem is with 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, which can be manipulated through blunt pressure or incision. Real-time topologic changes are also supported.

For the moment, a good alternate 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 the 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, 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. New methods of surgical training exist, however, that can help to reduce error and risk to the patient.[198,199]

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 virtual instructor or can be monitored and proctored by a real instructor. This means that the student can learn on his or her own time, outside of the operating room.[200]

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," which 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