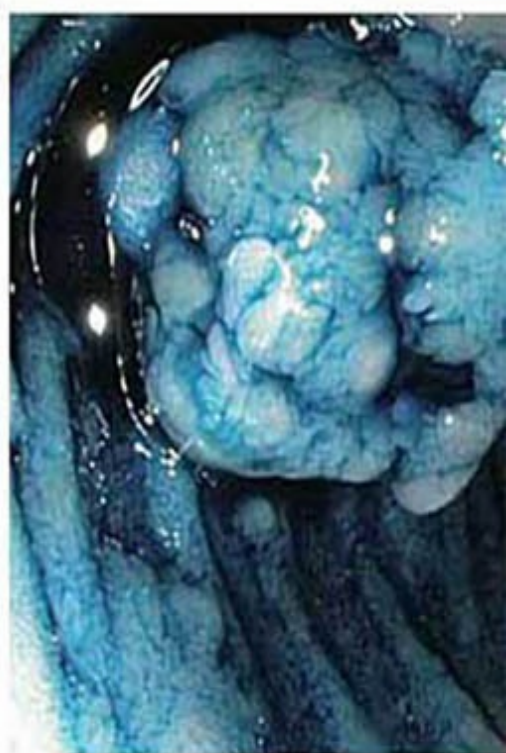
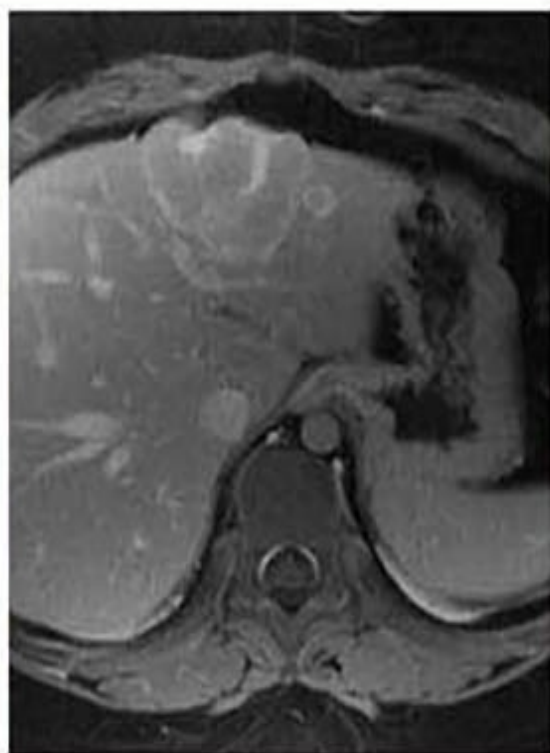
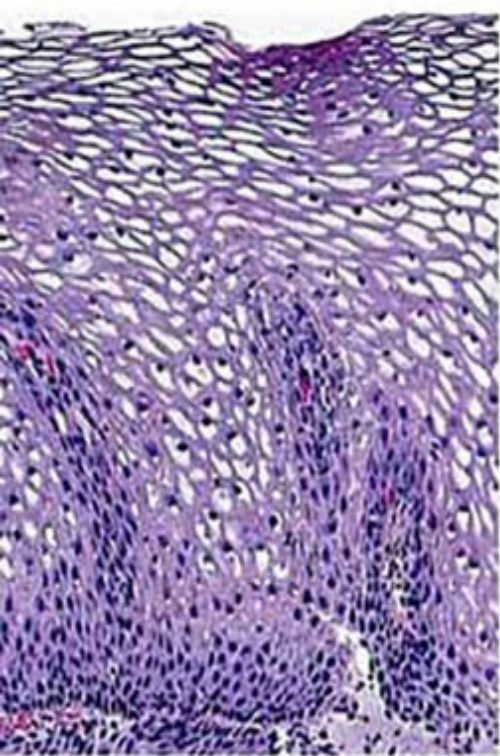


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**WALKER'S
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GASTROINTESTINAL DISEASE**

**PATHOPHYSIOLOGY • DIAGNOSIS •
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SIXTH EDITION

WALKER'S PEDIATRIC GASTROINTESTINAL DISEASE

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SIXTH EDITION

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DEDICATIONS

With deepest gratitude to Allan Walker who has mentored and supported me for all of my professional life. And to my family, Martha, Emily, Scott, Ellie, Avery, Adam, Monica, Maya and Jesse for their constant love and support.

—Ronald E. Kleinman, MD

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—Ian R. Sanderson, MD

This book is dedicated to trainees—past, current, and future—who make the journey through life in academic medicine so interesting, meaningful, and rewarding.

—Philip M. Sherman, MD

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Persistent and Chronic Diarrhea (15.2b)

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University of Chicago, Pritzker School of Medicine

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Northshore University Health System

Evanston, Illinois

Necrotizing Enterocolitis (20.3)

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Visiting Scientist

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Biology Research Center
Massachusetts General Hospital for Children
Harvard Medical School
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Department of Pediatrics
Università Politecnica delle Marche
Ancona, Italy
Celiac Disease (16.1)

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Department of Pediatric Gastroenterology
Hôpital Universitaire Robert Debré
Paris, France
Normal Physiology of Intestinal Digestion and Absorption (15.1)

Mei-Wei Chang, PhD, RN

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Michigan State University
East Lansing, Michigan
Hepatitis B Virus (30.1a)

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Professor, Department of Radiology
University of Toronto
Division Head of Nuclear Medicine
Head of Research for Diagnostic Imaging
Senior Associate Scientist, Research Institute
The Hospital for Sick Children
Toronto, Ontario, Canada
Radionuclide Scintigraphy (49.4)

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Division of Gastroenterology
Department of Pediatrics
Chang Gung Memorial Hospital
Taoyuan, Taiwan

Inflammation (20.1)

Jaime Chu, MD

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Icahn School of Medicine at Mount Sinai
Pediatric Hepatology and Liver Transplantation
Mt. Sinai Hospital
New York, New York
Other Viral Infections (30.1c)

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The Ohio State University College of Medicine
Division of Gastroenterology, Hepatology and Nutrition
Nationwide Children's Hospital
Columbus, Ohio
Hirschsprung Disease (23.2b)

Erika C. Claud, MD

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Departments of Pediatrics and Medicine
Sections of Neonatology and Gastroenterology
The University of Chicago School of Medicine
Chicago, Illinois
Necrotizing Enterocolitis (20.3)

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University of Alabama at Birmingham School of Medicine
Physician-in-Chief and Director
Gastroenterology, Hepatology and Nutrition
Children's of Alabama
Birmingham, Alabama
Bacterial Infections, Food- and Waterborne Infections (19.2a)
Viral Infections (19.2b)

Andrew B. Cooper, PhD

School of Resource and Environmental Management
Simon Fraser University
Burnaby, British Columbia, Canada
The Statistics and Interpretation of Screening and Diagnostic Tests (54)

Catherine Cord-Udy, MBBS, FRACS

Pediatric Surgeon
Women's and Children's Hospital
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The Pediatric Ostomy (17.3)

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Reader and Consultant Pediatric Gastroenterologist
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Barts and The London School of Medicine and Dentistry
Queen Mary University of London
London, United Kingdom
Ulcerative and Indeterminate Colitis (20.4b)

Salvatore Cucchiara, PhD

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Pediatric Gastroenterology and Liver Unit
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Rome, Italy
*Normal Motility and Development of the Esophageal Neuroenteric System
(4.1)*

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*Drs. Rouben and Violet Jiji Professor of Pediatrics
Chair, Department of Pediatrics
Director of the University of Maryland Children's Hospital
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Inflammation (20.1)*

Mark Davenport, MD

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The Liver: Anatomy and Embryology (26)

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Head, Department of Pediatrics
University of Otago, Christchurch
Dunedin, New Zealand
Other Causes of Gastritis (9.3)

Gustavo Andrade de Paulo, MD, PhD

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Cancer Institute of São Paulo
Universidade Federal de São Paulo
São Paulo, Brazil
Endoscopic Retrograde Cholangiopancreatography (44.5)

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Team Leader, Physiology and Experimental Biology of Heart and Muscles
University of Montpellier
Montpellier, France
Anatomy and Embryology (12)

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Director, Pediatric Liver, Gastroenterology, and Nutrition Center
Clinical Director of Child Health
King's College Hospital
London, United Kingdom
Acute Liver Failure (37)

Carlo Di Lorenzo, MD

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Ohio State University College of Medicine

Division Chief, Gastroenterology, Hepatology and Nutrition
Medical Director, Center for Colorectal and Pelvic Reconstruction
Nationwide Children's Hospital
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Normal Motility and Development of the Gastric Neuroenteric System
(11.1)
Gastric Motility Disorders (11.2)

Giovanni Di Nardo, MD

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*Ch. 4.1: Normal Motility and Development of the Esophageal
Neuroenteric System*

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Genetic Testing in Clinical Practice (54.1)

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The Research Institute
Department of Gastroenterology, Hepatology and Nutrition
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Shwachman-Diamond Syndrome (43.2)

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Clinical Assistant Professor of Surgery
University of Arizona College of Medicine
Instructor of Surgery, Mayo Clinic
Surgical Director, Pediatric Intensive Care Unit

Phoenix Children's Hospital
Phoenix, Arizona
Appendicitis (17.2)

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Pediatric Gastroenterology
Director of Pediatric Liver Transplants
Mayo Clinic Rochester
Rochester, Minnesota
Systemic Conditions Affecting the Liver (36)

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Director, Mucosal Immunology and Biology Research Center
Associate Chief for Basic, Clinical, and Translational Research
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Celiac Disease (16.1)

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Oregon Health and Science University
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Intestinal Obstructions (17.1)

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Chief Emeritus, Pathology Service, Texas Children's Hospital
Pathologist Reviewer, Children's Oncology Group
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Liver Tumors (33)

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Department of Clinical Science and Education
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Stockholm, Sweden
Short-Bowel Syndrome (21.1)

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Molecular Medicine, Case Western Reserve University
Department of Pathobiology
Cleveland Clinic Lerner Research Institute
Cleveland, Ohio
Inflammation (20.1)

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Henry Ford Hospital
Clinton Township, Michigan
Benign Perianal Lesions (18)

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Director of Liver Diseases and Transplant Program
Professor, Departments of Surgery and Pediatrics
MedStar Georgetown Transplant Institute
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Intestinal Transplantation (21.3)

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Associate Professor of Pediatrics, Baylor College of Medicine
Director, Gastrointestinal Endoscopy and Therapeutic Endoscopy
Medical Director, Pancreaticobiliary Program
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Endoscopic Retrograde Cholangiopancreatography (44.5)

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Hemochromatosis (34.9)

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Director of Center for Innovative Regenerative Therapies
Children's Hospital of Pittsburgh of UPMC
Medical Director, McGowan Institute for Regenerative Medicine
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Normal Hepatocyte Function and Mechanisms of Dysfunction (27.4)

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Associate Professor of Pediatrics, Harvard Medical School
Director, Gastrointestinal Endoscopy
Director, Pediatric Polyposis Program
Medical Director, Gastroenterology Procedure Unit;
Co-Director, Pancreatic Disorders Program
Boston Children's Hospital
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Patient Preparation and General Considerations (44.1)
Gastrointestinal Endosonography (44.4)

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Radiation-Induced Bowel Injury (25.2)

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Systemic Conditions Affecting the Liver (36)

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Eosinophilic Gastrointestinal Disease (16.2a)

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Hirschsprung Disease (23.2b)

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Imaging of Gastrointestinal Tract Disease (49.1)

Cross-Sectional Imaging of Abdominal Masses (49.2)

Interventional Gastrointestinal Radiography (49.3)

Debra A. Gervais, MD

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Massachusetts General Hospital for Children
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Imaging of Gastrointestinal Tract Disease (49.1)

Cross-Sectional Imaging of Abdominal Masses (49.2)

Interventional Gastrointestinal Radiography (40.3)

Glenn R. Gibson, PhD

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Reading, United Kingdom
Research Scientist at MRC Dunn Clinical Nutrition Center
Cambridge, United Kingdom
Prebiotics: Composition and Potential Functions (19.1b)

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Upper Gastrointestinal Bleeding (44.2b)

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Atypical Colitis and Other Inflammatory Diseases (20.4c)

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Other Esophageal Neuromuscular Disorders (4.3)

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Acid-Peptic Disease (9.2)

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Department Pediatric Gastroenterology, Hepatology and Nutrition

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Necker-Enfants Malades Hospital

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Congenital Enteropathies (15.3c)

Autoimmune Enteropathy and IPEX Syndrome (16.3)

Short Bowel Syndrome (21.1)

Glenn R. Gourley, MD, AGAF

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Bilirubin Metabolism (27.2)

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Microbiology

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Lysosomal Acid Lipase Deficiencies (34.7)

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Crohn's Disease (20.4a)

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Acute Diarrhea (15.2a)

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Persistent and Chronic Diarrhea (15.2b)

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Peritonitis and Intra-abdominal Abscesses (20.5)

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Immune Deficiency and the Liver (30.3)

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Gastroesophageal Reflux (4.2)

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Gastrointestinal Manifestations of Immunodeficiency Disorders (20.2)

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Professor of Global Health
Professor of Medicine in Infectious Diseases
Boston University School of Public Health
Chief, Division of Global Health
Massachusetts General Hospital
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The Statistics and Interpretation of Screening and Diagnostic Tests (54)

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Consultant Surgeon, St Vincent's Public Hospital and the Royal
Melbourne Hospital
Upper Gastrointestinal and Bariatric Surgeon
Parkville, Victoria, Australia
Pancreatic Tumors (41)

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Associate Dean, Clinical and Translational Research
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University of Cincinnati College of Medicine
Director, Division of Gastroenterology, Hepatology and Nutrition,
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Bile Acid Synthesis and Metabolism (34.11)

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Division of Gastroenterology, Hepatology, and Nutrition
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Disorders of Carbohydrate Metabolism (34.2)

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University College Dublin
Dublin, Ireland
Ch. 19.1: Microbial Interactions with Gut Epithelium (19.1)

Paul E. Hyman, MD

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Children's Hospital of New Orleans
Louisiana State University Health Sciences Center
New Orleans, Louisiana
Gastrointestinal Features of Pediatric Illness Falsification (50)

Samar Ibrahim, MB, ChB

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Consultant, Division of Pediatric Gastroenterology and Hepatology
Department of Pediatric and Adolescent Medicine
Consultant, Division of Gastroenterology and Hepatology
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Systemic Conditions Affecting the Liver (36)

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Intestinal Transplantation (20.4)

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The Hospital for Sick Children
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Drug-Induced Bowel Injury (25.1)

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Benign Perianal Lesions (18)

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Appendicitis (17.2)

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Kapiolani Medical Center for Women and Children
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Benign Perianal Lesions (18)

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Microbial Interactions with Gut Epithelium (19.1)

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Intestinal Transplantation (21.3)

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Bile Formation and Cholestasis (27.1)

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Intestinal Transplantation (21.3)

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Parasitic and Fungal Infections (19.2c)

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Genetic Testing (34.1)

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Congenital Anomalies Including Hernias (13)

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Esophageal and Gastric Polyps and Neoplasms (10)

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Atypical Colitis and Other Inflammatory Diseases (20.4c)

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Liver Biopsy Interpretation (45)

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Prebiotics: Composition and Potential Functions (19.1b)

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Medical College of Wisconsin
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Nausea, Vomiting, and Pyloric Stenosis (8)

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Surgical Aspects of Inflammatory Bowel Disease in Children (20.4d)

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Other Causes of Gastritis (9.3)

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Hepatitis C Virus (30.1b)

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Nausea, Vomiting, and Pyloric Stenosis (8)

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Eosinophilic Gastrointestinal Diseases (16.2a)

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Small-Bowel Bacterial Overgrowth (19.2d)

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Outcomes Research in Pediatric Gastroenterology (53)

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Endoscopic Retrograde Cholangiopancreatography (44.5)

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Crohn's Disease (20.4a)

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Pancreatitis Acute and Chronic (42.1)

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Appendicitis (17.2)

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Probiotics (19.1a)

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Congenital Intestinal Transport Defects (15.3b)

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*Normal Motility and Development of the
Intestinal Neurenteric System (23.1)*

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Traumatic and Toxic Injury of the Esophagus (6)

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Intestinal Tranplantation (21.3)

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Treatment of End-Stage Liver Disease (38)

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Outcomes Research on Diagnostic and Therapeutic Procedures (53)

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Eosinophilic Esophagitis (16.2a)

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Lower Gastrointestinal Bleeding (44.3b)

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Antimicrobials (19.1c)

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Benign Perianal Lesions (18)

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Juvenile Tropical Pancreatitis (42.2)

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Intestinal Polyps and Polyposis (22.1)

Endoscopic Retrograde Cholangiopancreatography (44.5)

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Food Allergic Enteropathy (16.2b)

Upper Gastrointestinal Endoscopy (44.2a)

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Amino Acid Metabolism (34.3)

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Genetically Determined Disaccharides Deficiency (15.3a)

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Fatty Liver Disease in Children (35)

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Gastrointestinal Manometry (47)

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Normal Motility and Development of the Esophageal Neuroenteric System (4.1)

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Toxic and Traumatic Injury of the Esophagus (6)

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Intestinal Polyps and Polyposis (22.1)

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Other Causes of Gastritis (9.3)

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Ethics and Regulatory Issues (55)

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Gastroenterology and Hepatology
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Director, Pediatric IBD program
Yale School of Medicine
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Bacterial, Parasitic, and Other Infections (30.2)

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 α_1 -Antitrypsin Deficiency (34.5)

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Intestinal Failure–Associated Liver Disease (21.2)

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(11.1)*

Motility Disorders (11.2)

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Genetically Determined Disaccharides Deficiency (15.3a)

PREFACE

As I look back on the five previous editions of this textbook, I recognize how much the field has expanded and the importance of our understanding gastrointestinal diseases within the context of ongoing development of infants and children. This edition of the textbook will be published later than previous editions, which have been linked to the Pediatric Gastroenterology World Congresses occurring every four years since 2000. This is due to a change in publishers. People's Medical Publishing House—USA will now be publishing this textbook as well as its companion text, entitled *Nutrition in Pediatrics* (5th edition). In addition, new sections have been added to reflect the expanding complexity of the field, particularly new techniques now used to accurately establish complex diagnoses.

It is now apparent that pathophysiologic occurrences during infancy, and even during the intrauterine period, may have a profound effect on the expression of disease in later life. Two hypotheses, the Barker hypothesis (fetal programming) and the hygiene hypothesis, which have now been generally accepted, strongly suggest the importance of fetal nutrition and neonatal colonization on the enhanced incidence of metabolic and immunologic diseases increasingly prevalent in developed countries. This is strongly illustrated by the pediatric complications of maternal obesity during pregnancy and the increased incidence of Cesarean section delivery of the newborn for the convenience of the obstetrician and parents at the expense of adequate initial colonization for the newborn infant. Accordingly, this edition of *Pediatric Gastrointestinal Disease* and its companion *Pediatric Nutrition* devote new chapters to the adequate nutrition beginning in *utero* and the colonization of the newborn intestine and its disease consequences.

As with previous editions, the size and content of each section has been modified and new chapters added to reflect an increasing evolution of subspecialty programs within gastroenterology and a better understanding of subspecialty conditions (motility, inflammation, and autoimmune bowel disease) that have emerged in pediatric gastroenterology. As the importance of genetics and molecular biology in the pathophysiology and diagnosis of complex pediatric conditions of the gut, pancreas, and liver have become appreciated, expanded chapters cover their importance in the field. Furthermore, a more comprehensive representation of world leaders in pediatric gastroenterology among the editors of this edition have expanded the authorship to reflect experts in specific diseases within various continents rather than principally in North America. In other words, the edition is dedicated to a comprehensive, worldwide approach to the practice of pediatric gastroenterology.

Finally, as occurs in many rapidly expanding medical fields, difficult decisions are required before treatment of complex gastrointestinal conditions can be recommended that are based on clinical evidence. These therapeutic approaches require large, multi-centered, randomly controlled, single-protocol studies. Accordingly, many pediatric gastroenterologists are now resorting to clinical investigation to answer their therapeutic needs. In this edition, two comprehensive chapters on principles of clinical investigation are provided, and then, in an endeavor to be inclusive, another chapter on ethics and regulatory considerations is included. In addition, psychosocial aspects of gastrointestinal disease are provided in three chapters that consider the physiologic components of intestinal disease.

The editors have provided an excellent background for an approach to evaluating children with gastrointestinal disease in the 21st century. I have been honored to be part of this approach.

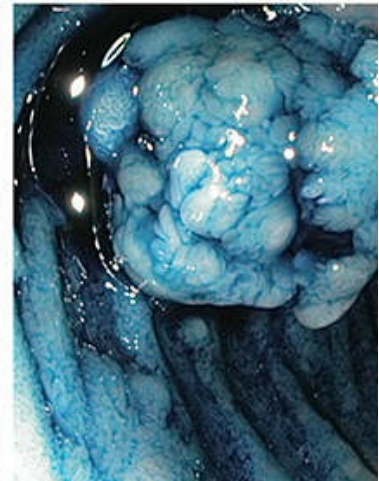
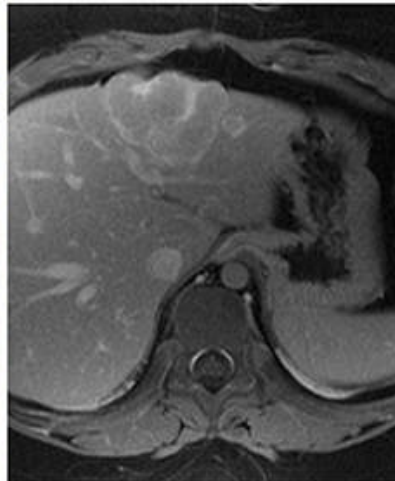
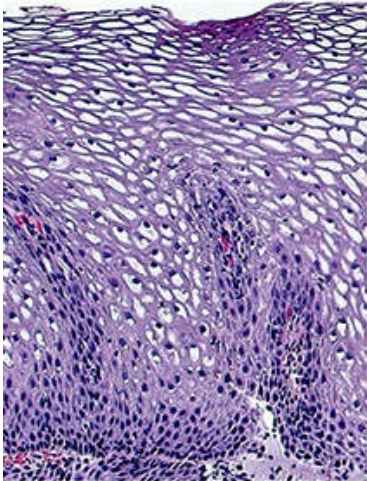
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I

Mouth and Esophagus

1

Anatomy, Embryology, Congenital Anomalies of the Mouth and Esophagus

Jonathan E. Teitelbaum, MD

Congenital anomalies of the mouth and esophagus are relatively common. The majority of these anomalies are readily apparent at birth or, in many cases, can be appreciated on prenatal ultrasonography. Our understanding of the embryology of the mouth and esophagus and the associated genes and gene products has increased rapidly over the past decade. With that, there has been a rapid advancement in identifying various genetic mutations that result in abnormalities of development and their phenotypic expression. Whereas some malformations are clinically silent, others can cause difficulties in feeding, articulation, or even life-threatening respiratory difficulties. More complex malformations often require support from multidisciplinary teams, including surgeons (general, otolaryngologic, orthodontic), gastroenterologists, speech pathologists, and geneticists.

FACIAL CLEFTS (CLEFT LIP AND CLEFT PALATE)

Oral clefts are among the most common of all birth defects, second only to clubfoot. Cleft lip with or without cleft palate [CL(P)] occurs with an incidence of 1 in 500 to 1 in 2,500 in different populations based on ethnic group, geographic location, and socioeconomic conditions.¹ The highest incidence is among Native Americans (3.6 in 1,000 live births), whereas

among blacks, it is less (0.3 in 1,000 live births). Whites have an incidence of 1 in 1,000 live births. Defects are unilateral in 80%.²

Isolated cleft palate (CP) occurs in approximately 1 in 2,000 live births, and there is little to no racial preponderance.² CL(P) is more common in boys, whereas CP is seen more commonly in girls. The cause is likely multifactorial disruption of embryologic morphogenesis.² Higher birth order may also be a risk factor for CL(P) and CP. However, studies are not conclusive and may be confounded by other factors, such as advanced maternal or paternal age or increased exposure to teratogens, which, in themselves, may be risk factors.³ While nonsyndromic clefts are generally believed to be relatively benign conditions, a study shows that the perinatal mortality rate for babies with isolated facial clefts was significantly higher than the background population (odds ratio 3.3).⁴

The risk of having subsequent children with clefts is different for those with CL(P) from those with CP. When both parents are unaffected and have an affected child, the risk of recurrence is 4.4% for CL(P) and 2.5% for CP. If one parent is affected, the risk is increased to 15.8% for CL(P) and 14.9% for CP. If two children are affected and the parents are unaffected, the risk for a third child is 9% for CL(P) and 1% for CP.² Concordance among monozygotic twins ranges between 40% and 60%, whereas it is 5% among dizygotic twins. The lack of 100% concordance rates among monozygotic twins argues against genetic events alone being responsible for the clefting phenotype.⁵

Cleft lip is a unilateral or bilateral gap in the upper lip and jaw, which form during the third to seventh week of embryologic development.¹ The incisive foramen divides the hard palate into a primary and secondary palate. The primary palate lies anterior to the incisive foramen and includes the bony premaxilla, mucoperiosteal covering, and incisor teeth. The secondary palate is posterior to the incisive foramen and is composed of horizontal plates of the maxilla and palatine bone. The remaining dentition arrives from the secondary palate. Primary palate formation begins at four to five weeks gestation with the fusion of the paired median nasal prominences. This marks the separation of the oral and nasal cavities. Ultimately, the median nasal prominences give rise to the dental arch, incisor teeth, and philtrum of the upper lip. Formation of the secondary palate (hard and soft) begins at approximately the seventh week of gestation. The posterior maxillary prominences form palatal shelves, which rotate inferiorly and medially to fuse with the vomer in the midline. Anterior to posterior palatal closure occurs in a zipper-like fashion. At nine

weeks gestation, the hard palate fuses with the septum to complete the separation of the oral and nasal cavities. The soft palate is composed of five paired muscles: tensor veli palatini, levator veli palatini, palatoglossus, palatopharyngeus, and musculus uvulae. Midline approximation of the soft palatal musculature marks the completion of palatogenesis at approximately 12 weeks gestation.²

The multifactorial inheritance model is currently the most widely accepted theory of nonsyndromic clefts. In this model, the risk of developing a given anomaly is determined by the presence of either genetic or environmental liabilities. Each liability occurs in a normal distribution within the population. The accumulation of multiple small liabilities eventually reaches a threshold, beyond which a defect occurs. Variable penetrance of the phenotype for many genes results in non-Mendelian inheritance patterns. Ongoing research is investigating the role that associated features play in the familial transmission patterns of nonsyndromic clefts. Associated features include fluctuating and directional asymmetry, left handedness, dermatoglyphic patterns, craniofacial morphology, orbicularis oris muscle defects, structural brain and vertebral anomalies, minor physical anomalies, and velopharyngeal incompetence.⁶

An estimated 300 syndromes include CL(P) in their phenotype; however, syndromic clefts account for only 30% of CL(P).¹ The proportion of patients with CP who are syndromic versus nonsyndromic remains unresolved, with estimates varying widely, between 15% and 80%.¹ Approximately 25% of syndromic clefts are associated with Stickler syndrome, whereas another 15% are associated with velocardiofacial syndrome.² The most common malformations in association with clefts are found in the central nervous system and the skeletal system, followed by the urogenital and cardiovascular systems.⁷ Various syndromes associated with CP (Table 1-1) and CL(P) (Table 1-2) have been described.

Defects in the PVRL1 gene (chromosome 11q23) result in abnormal formation of nectin 1, a cell–cell adhesion molecule expressed in the developing face and palate that is essential for fusion of the medial edge epithelia. A 50% reduction in the amount of nectin 1 appears to be a risk factor for nonsyndromic CL(P) in patients in Margarita Island and Venezuela.¹ A similar gene, OFC3 (19q13, MIM#600757), has also been implicated in nonsyndromic CL(P) based on genetic linkage studies. Other candidate genes include OFC1 (6p24.3, MIM #119530), OFC2 (2p13, MIM #602966), OFC4 (4q, MIM#608371), OFC5 (MSX1, 4p16.1, MIM

#608874), OFC6 (MIM#608864), TP63 (3q27), TGFA (2p13), TBX22,1 PGD1 (1p36), 6 methylenetetrahydrofolate reductase (1q36),^{8,9} transcobalamin 2,¹⁰ and TGFalpha (2p13).⁸ A defect in the CDH1/E-cadherin gene (MIM#192090) has been associated with CL(P) and hereditary diffuse gastric cancer.¹¹

The causative role of teratogens in the formation of clefts has been supported by studies of maternal exposures to corticosteroids, phenytoin, valproic acid,⁵ thalidomide,⁵ alcohol,⁵ cigarettes,⁵ dioxin,⁵ or retinoic acid. In addition, maternal diabetes mellitus, hormone imbalance, and various vitamin and trace mineral deficiencies have been associated with clefts in the offspring.¹² Although there is no consensus that any particular teratogen or environmental factor is implicated in most clefts,¹ some studies suggest that the risk may be increased with exposure to oxygenated (odds ratio 1.8), chlorinated (odds ratio 9.4), and petroleum (odds ratio 3.6) solvents.¹³ Folic acid may have a protective effect to reduce the risk of clefting, although this is controversial.^{8,14} Studies suggest that maternal zinc deficiency may also be associated with nonsyndromic clefting.^{15,16}

Prenatal diagnosis allows for early parental counseling. Current technology can detect CL(P) at 15 weeks gestation because the soft tissues of the fetal face become distinct to transabdominal ultrasonography.⁷ During the second trimester, ultrasonography detects less than 20% of cases of isolated CL(P) and far fewer cases of isolated CP.⁷ However, syndromic CL(P) is detected in more than 30%, perhaps because a more detailed scan is undertaken given the associated anomalies, or because these clefts are larger and more readily visualized. Optimum timing for diagnosis is between 20 and 22 weeks gestation. The ability to see the defect is influenced by the position of the fetus, position of an overlying hand or umbilical cord, maternal obesity, multiple pregnancies, oligohydramnios, and the experience of the technician. The use of transvaginal ultrasonography and three-dimensional ultrasonography also increases the sensitivity and specificity of the test.² Real-time magnetic resonance imaging (MRI) has also been proven useful in prenatal diagnosis of CP.¹⁷ A delay of greater than 24 hours in diagnosis of nonsyndromic CP without cleft lip in the newborn can occur in as much as 37%.¹⁸ Those with a delay in diagnosis often had feeding problems or nasal regurgitation. The authors suggest that all newborns should undergo visual inspection of the palate as palpation alone is inadequate.

TABLE 1-1 Cleft Palate or Bifid Uvula Without Cleft Lip

Syndrome	OMIM Number^a
Catel-Manzke	302380
Cerebrocostomandibular	117650
Deletion 4q	
Dubowitz	223370
Duplication 3q	
Duplication 10q	
Escobar	265000
Femoral hypoplasia–unusual facies	134780
Fibrochondrogenesis	228520
Hay-Wells syndrome of ectodermal dysplasia	106260
Hydrolethalus	236680
Kabuki make-up	147920
Kniest dysplasia	156550
Marden–Walker	248700
Meckel–Gruber	249000
Nager	154400
Orofaciodigital	311200
Otopalatodigital, type I	311300
Otopalatodigital, type II	304120

Popliteal pterygium	119500
Retinoic acid embryopathy	243440
Short-rib polydactyly, type II	263520
Velocardiofacial	192430
Spondyloepiphyseal dysplasia congenita	183900
Stickler 1	08300
Treacher Collins	154500
Van der Woude	119300

^aSearching the OMIM (Online Mendelian Inheritance in Man) can be done at <http://www3.ncbi.nlm.nih.gov/omim/>.

Source: Adapted from Jones.¹²⁰

TABLE 1-2 Syndromes With Cleft Lip With or Without Cleft Palate

Syndrome	OMIM Number ^a
Deletion 4p	
Ectrodactyly–ectodermal dysplasia–clefting	604292
Fryns	229850
Hay-Wells syndrome of ectodermal dysplasia	106260
Holoprosencephaly sequence	157170
Miller	247200
Mohr	252100
Orofaciodigital	311200

Popliteal pterygium	119500
Rapp-Hodgkin ectodermal dysplasia	129400
Roberts	268300
Short-rib polydactyly, type II	263520
Trisomy 13	
Van der Woude	119300

^aSearching the OMIM (Online Mendelian Inheritance in Man) can be done at <http://www3.ncbi.nlm.nih.gov/omim/>.

Source: Adapted from Jones.¹²⁰

Initial evaluation of a patient with CP should include prenatal care, birth history, teratogen exposure, and a family history of clefting or syndromes. A multidisciplinary team is often helpful in assessing the family's medical and psychosocial needs. The cleft team should consist of a maxillofacial or plastic surgeon, otolaryngologist, audiologist, dentist (orthodontist or oral surgeon), social worker, geneticist, pediatrician, nutritionist, and speech pathologist. Breastfeeding is possible in some patients with a short or narrow cleft.¹⁹ Infants with larger clefts can rarely generate adequate suction for traditional breastfeeding or bottle feeding. Various specialized nipples have been created to facilitate feeding. Feeding typically takes longer, and frequent burping may be required in these infants because they often swallow large amounts of air. Infants should be weighed on a weekly basis initially to ensure adequate intake.² Evidence suggests that children with CL have a lesser degree of weight and length impairment in the first few years of life compared to those children with cleft lip and palate or CP.²⁰

Palatal clefting disrupts all layers of the normal palate architecture, including mucosa, muscle, and bone. The muscles of the soft palate must wrap anteriorly and insert on the cleft margin or the posterior palate. Aberrant tensor veli palatini insertion results in eustachian tube dysfunction, so nearly all CP patients will have chronic otitis media requiring myringotomy tube placement. Abnormal insertion of the levator veli palatini results in loss of normal velopharyngeal competence.²

CP may be classified as primary or secondary, complete or incomplete, unilateral or bilateral, or submucous. Primary CP results in incomplete closure of the hard palate anterior to the incisive foramen, whereas secondary CP results in a midline defect posterior to the incisive foramen. Secondary clefts appear to be distinct genetic entities, unrelated to cleft lip but often associated with Pierre Robin sequence (PRS). Complete CP involves the primary secondary and soft palate and is usually associated with cleft lip. Submucous CP results from inadequate development of the muscles of the soft palate without disruption of the mucosa. They can characteristically include a bifid uvula, dehiscence of the central palatal musculature (may be palpable or result in bluish discoloration in the midline, termed a zona pellucida), and loss of the posterior nasal spine.²

Presurgical orthopedic techniques are used to modify the shape of the cleft deformity before definitive cleft repair. These increase the ease of the primary repair, normalize facial growth, and prevent alveolar collapse. Active techniques include finger massage, lip taping and strapping, and oral prosthetics. Passive techniques are aimed at inhibiting tongue protrusion between the palatal shelves by using oral obturators. Although these techniques have been shown to effectively narrow the distance between alveolar segments, no differences in esthetic outcome, need for revision surgery, or improvement in feeding have been prospectively demonstrated.²

Palatoplasty aims to separate the oral and nasal cavities and restore velopharyngeal competence. An aggressive approach must be balanced with the risk of maxillary growth disturbance.²

Although 90% of patients with a cleft lip have repair between 3 and 6 months of age,²¹ the timing of CP repair is controversial. Proponents of early CP repair (3–6 months) believe that early velopharyngeal competence is critical to normal speech development. Proponents of late palatal repair (2–15 years) believe that the risk of iatrogenic disruption of palatal growth and midfacial hypoplasia outweighs the risk of speech abnormalities. Clefts delayed for more than two years generally require obturation to overcome velopharyngeal incompetence and allow normal speech development. Oral obturators placed prior to two years are often poorly tolerated. The lack of clear evidence supporting early versus late repair has led to a compromise in which most surgeons perform repair from 12 to 24 months.² Experience with neonatal cleft lip and palate repair has been described as safe, although long-term follow-up is not yet available.²² Fetal surgery for CL(P) has also been described.²³ The risks