Volume 40

Advances in Pediatrics®

Barness • DeVivo Kaback • Morrow Oski • Rudolph

Advances in **Pediatrics**®

Editor

Lewis A. Barness, M.D.

Professor of Pediatrics, Department of Pediatrics, University of South Florida College of Medicine, Tampa; Emeritus Professor, University of Wisconsin, Madison

Associate Editors Darryl C. DeVivo, M.D.

Sidney Carter Professor of Neurology, Professor of Pediatrics, Columbia University College of Physicians and Surgeons; Director, Pediatric Neurology, Attending Pediatrician and Neurologist, Neurological Institute and Babies Hospital, Presbyterian Hospital, New York, New York

Michael M. Kaback, M.D.

Professor and Chairman, Department of Pediatrics, University of California, San Diego, School of Medicine, La Jolla, California

Grant Morrow III, M.D.

Professor and Chairman, Department of Pediatrics, The Ohio State University College of Medicine; Medical Director, Children's Hospital, Columbus, Ohio

Frank A. Oski, M.D.

Chairman and Pediatrician-in-Chief, Department of Pediatrics, The Children's Center, Johns Hopkins Hospital, Baltimore, Maryland

Abraham M. Rudolph, M.D.

Chairman of Pediatrics, University of California Medical Center, San Francisco, California



Volume 40 · 1993



Sponsoring Editor: Kelly Poirier Project Manager: Denise Dungey Project Supervisor: Maria Nevinger Production Editor: Laura Pelehach

Staff Support Administrator: Barbara Kelly

Copyright © 1993 by Mosby-Year Book, Inc. A Year Book Medical Publishers imprint of Mosby-Year Book, Inc.

Mosby-Year Book, Inc. 11830 Westline Industrial Drive St. Louis, MO 63146

All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, recording, or otherwise, without prior written permission from the publisher. Printed in the United States of America.

Permission to photocopy or reproduce solely for internal or personal use is permitted for libraries or other users registered with the Copyright Clearance Center, provided that the base fee of \$4.00 per chapter plus \$.10 per page is paid directly to the Copyright Clearance Center, 21 Congress Street, Salem, MA 01970. This consent does not extend to other kinds of copying, such as copying for general distribution, or advertising or promotional purposes, for creating new collected works, or for resale.

Editorial Office: Mosby—Year Book, Inc. 200 North LaSalle St. Chicago, IL 60601

International Standard Serial Number: 0065-3101
International Standard Book Number 0-8151-0527-4

Contributors

Uri Alon, M.D.

Professor of Pediatrics, University of Missouri—Kansas City School of Medicine; Division of Pediatric Nephrology, The Children's Mercy Hospital, Kansas City, Missouri

Stephen Ashwal, M.D.

Department of Pediatrics, Division of Child Neurology, Loma Linda University School of Medicine, Loma Linda, California

Elia M. Ayoub, M.D.

Professor of Pediatrics, Department of Pediatrics, University of Florida College of Medicine, Gainesville, Florida

Michael D. Bailie, M.D., Ph.D.

Director, Senior Associate Dean, and Professor of Pediatrics, University of Illinois College of Medicine, Peoria, Illinois

H. Jorge Baluarte, M.D.

Professor of Pediatrics, Temple University School of Medicine, Chief, Section of Nephrology, St. Christopher's Hospital for Children, Philadelphia, Pennsylvania

Cheston M. Berlin, Jr., M.D.

University Professor of Pediatrics, Department of Pediatrics, Pennsylvania State University College of Medicine, The Milton S. Hershey Medical Center, Hershey, Pennsylvania

Karen Bresnahan, M.D.

Division of Developmental and Behavioral Pediatrics, Department of Pediatrics, Boston University School of Medicine/Boston City Hospital, Boston, Massachusetts

Peter R. Dallman, M.D.

Department of Pediatrics, University of California, San Francisco School of Medicine, San Francisco, California

Kenneth J. Ellis. Ph.D.

USDA/ARS Children's Nutrition Research Center, Department of Pediatrics, Baylor College of Medicine, Texas Children's Hospital, Houston, Texas

Deborah A. Frank, M.D.

Division of Developmental and Behavioral Pediatrics, Department of Pediatrics, Boston University School of Medicine/Boston City Hospital, Boston, Massachusetts

Alan B. Gruskin, M.D.

Chairman, Department of Pediatrics, Wayne State University School of Medicine, Pediatrician-In-Chief, Children's Hospital of Michigan, Detroit, Michigan

Stanley Hellerstein, M.D.

Professor of Pediatrics, University of Missouri—Kansas City, School of Medicine: Chief, Section of Nephrology, The Children's Mercy Hospital, Kansas City, Missouri

Richard Hong, M.D.

Professor of Pediatrics, Department of Pediatrics, University of Wisconsin Medical School, Madison, Wisconsin

Christina M. Iyama, M.D.

Assistant Professor of Pediatrics, Medical Director, Developmental Disabilities Clinic, Waisman Center, University of Wisconsin Medical School, Madison, Wisconsin

Bruce A. Kaiser, M.D.

Associate Professor of Pediatrics, Temple University School of Medicine, Section of Nephrology, St. Christopher's Hospital for Children, Philadelphia, Pennsylvania

Michael J. Landzberg, M.D.

Instructor of Pediatrics, Harvard Medical School, Assistant in Cardiology, Children's Hospital, Brigham & Women's Hospital, Boston, Massachusetts

Louisa Laue. M.D.

Department of Pediatrics, Georgetown University School of Medicine, Children's Medical Center, Washington, D.C.

Alexander K.C. Leung, M.B.B.S., F.R.C.P.(C), F.R.C.P.(Edin.)

Clinical Associate Professor, Department of Pediatrics, Faculty of Medicine, The University of Calgary, The Alberta Children's Hospital, Calgary, Alberta, Canada

James E. Lock, M.D.

Associate Professor of Pediatrics, Harvard Medical School, Chief, Clinical Cardiology, Children's Hospital, Boston, Massachusetts

Michael H. Malloy, M.D., M.S.

Professor of Pediatrics, University of Texas Medical Branch, Galveston, Texas

Herbert L. Needleman, M.D.

Professor of Psychiatry and Pediatrics, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania

Buford L. Nichols, Jr., M.D.

USDA/ARS Children's Nutrition Research Center, Department of Pediatrics, Baylor College of Medicine, Texas Children's Hospital, Houston, Texas

Ronald M. Perkin, M.D.

Department of Pediatrics, Division of Critical Care Medicine, Loma Linda University School of Medicine, Loma Linda, California

Martin S. Polinsky, M.D.

Associate Professor of Pediatrics, Temple University School of Medicine, Section of Nephrology, St. Christopher's Hospital for Children, Philadelphia, Pennsylvania

Mobeen H. Rathore, M.D.

Assistant Professor of Pediatrics, Department of Pediatrics, University of Florida College of Medicine, Gainesville, Florida

Owen M. Rennert, M.D.

Department of Pediatrics, Georgetown University School of Medicine, Children's Medical Center, Washington, D.C.

Peter D. Reuman, M.D.

Assistant Professor of Pediatrics, Department of Pediatrics, University of Florida College of Medicine, Gainesville, Florida

Wm. Lane M. Robson, M.D., F.R.C.P.(C), F.R.S.H.

Head, Division of Pediatric Nephrology, Department of Pediatrics, Faculty of Medicine, The University of Calgary, The Alberta Children's Hospital, Calgary, Alberta, Canada

Sanford Schneider, M.D.

Department of Pediatrics, Division of Child Neurology, Loma Linda University School of Medicine, Loma Linda, California

Joseph R. Thompson, M.D.

Department of Radiation Sciences, Section of Neuroradiology, Loma Linda University School of Medicine, Loma Linda, California

Lawrence G. Tomasi, M.D.

Department of Pediatrics, Division of Child Neurology, Loma Linda University School of Medicine, Loma Linda, California

Bradley A. Warady, M.D.

Associate Professor of Pediatrics, University of Missouri—Kansas City School of Medicine: Director of Dialysis and Transplantation, The Children's Mercy Hospital, Kansas City, Missouri

Barry S. Zuckerman, M.D.

Division of Developmental and Behavioral Pediatrics, Department of Pediatrics, Boston University School of Medicine/Boston City Hospital, Boston, Massachusetts

Preface

It is increasingly obvious that all of the yearly advances in pediatrics cannot be contained in one volume if sufficient space is allowed to explain them in adequate detail. Nonetheless, certain events appear worth documenting. This volume is particularly filled with such landmark advances.

Explosion is an inadequate word to describe the advances in genetic technology. Laue and Rennert describe the basic techniques of this decade

and expand by example practical approaches.

Fantastic developments are occurring in childhood immunizations. Reuman, Rathore, and Ayoub bring the latest information on what is available now and recommended schedules, what to expect in the near future, what is on the horizon, and the basis of developing new agents.

Frank, Bresnahan, and Zuckerman investigated a large number of infants born of cocaine-using mothers and find that the hysteria magnified by the media and some physicians is unwarranted. No "cocaine-baby" syndrome was detected; rather there appeared to be multiple ill effects from poor prenatal care fueled by the addicted mother. Addiction is explained,

together with some suggestions for treatment.

Organ transplantation is a therapeutic measure that accounts for major utilization of hospital beds and of medical dollars. Effectiveness in prolonging life and in some, affecting cure, is unquestioned. In *Advances in Pediatrics*, volume 30, 1983, bone marrow transplantation was discussed. Now, 10 years later in this volume, Hong discusses the cures and also the problems of bone marrow transplantation. One is elated when reading of the successes, but cannot avoid the feeling, when reading the complications, that medical transplant practitioners of the present era will be viewed in the future with similar alarm and derision as medical bloodletting or high colonic enema therapists of the past are viewed by us.

The changing meaning of lead poisoning is documented by Needleman. Also mentioned is his personal tribulation related to political and economic

interests in removal of lead exposure.

Alkalosis follows chloride depletion and was found to occur in infants fed a low-chloride formula. Infants who became alkalotic were noted to have developmental delay (Roy, Advances in Pediatrics, volume 31, 1984). Malloy attempts to determine whether delay also occurs in those who consumed the formula but did not develop alkalosis. Since many infants fed the soy-based formula had some prior difficulty, any noted delay had to be compared with those fed other soy formulas. It appears that those not becoming alkalotic have little or no differences from those fed other soy formulas.

Ellis and Nichols summarize reference body composition data and methods of determining body composition. Formerly an interesting research tool, body composition is recognized as important in evaluating obesity,

weight loss, athletic potential, growth hormone effects, aging, and osteoporosis.

Ashwal, Perkin, Thompson, Schneider, and Tomasi explore in detail cerebral blood flow and cerebral spinal fluid dynamics in children with meningitis. As development of antibiotics races against bacterial resistance and use of dexamethasone early in treatment finds it place, better understanding of the pathophysiology can be expected to bring further changes in therapy.

Separated from the basket of causes of mental retardation is the poorly understood but recently classified "Rett" syndrome. Iyama summarizes present knowledge including that of causes and directions for research, and she concludes with a plea for tolerance.

Balloons for occluding vascular lesions discussed by Rao in *Advances in Pediatrics*, volume 37, 1990, and parachutes for congenital heart lesions discussed by Landzberg and Lock in the present volume, confirm the advent of interventional cardiology. A new outlook is available for patients and physicians as decreased morbidity and mortality occur in children with previously horrendous outlook.

This volume contains three articles discussing significant advances in understanding and treating diseases of the kidney.

New diuretics with changing specificity are regularly introduced into the market. Together with use in high-risk infants and changing indications, Bailie carefully reviews the dos and don'ts of the most popular of these agents.

Advances in pathological techniques have led to more precise diagnosis of children with the nephrotic syndrome. Robson and Leung describe how these advances improve treatment and, equally important, improve prediction of course and outcome. They emphasize need of counseling parents and children afflicted with chronic diseases.

Treatment of the vasculitides affecting the kidney has undergone marked changes in the past decade. Alon, Warady, and Hellerstein document the changes with improved results and discuss the pathophysiology on which these are based. Their article here is a continuation of their discussion of the kidney in systemic disease. Their first article, The Kidney in Systemic Disease Part 1, appeared in volume 37 of Advances in Pediatrics.

Renal stones are relatively rare in children but their occurrence presents a challenge to the primary physician. Polinsky, Kaiser, Baluarte, and Gruskin present a clear, easy-to-follow approach to diagnosis, encompassing recent advances in understanding the pathogenesis of stone formation of diverse etiologies. Their suggestions for treatment are practical and frequently effective.

As anticipated by Holbrook and Christensen in *Advances in Pediatrics*, volume 38, 1992, erythropoietin is becoming a major boon in therapy. Dallman now documents the value of erythropoietin in decreasing the need for some transfusions in some prematurely born infants. More experience is needed.

Berlin has again covered pharmacologic advances. Since these reviews

have appeared regularly every 2 years in the even-numbered volumes, those volumes 30, 32, 34, 36, 38, and 40 provide an extensive review of most commonly used drugs and exposed toxins of children.

As always, your critiques and suggestions are welcome and appreciated.

Lewis A. Barness, M.D.

Contents

Contributors		vii
Preface		хi
Recombinant DNA Technology: A Clinical Revolution in Pediatrics.		1
By Louisa Laue and Owen M. Rennert		1
Concepts of Molecular Biology		1
Gene Structure, Function, and Organization		1
Techniques in Molecular Biology		3
Sex Chromosomes and Sexual Development		8
X Chromosome Inactivation: Turner Syndrome		8
SRY and TDF Genes: XX Males and XY Females		9
Maleness and the X Chromosome: Androgen Resistance		
Syndromes	,	10
Parental Disomy and Genomic Imprinting	,	11
Contiguous Gene Syndromes: Prader-Willi and Angelmann		
Syndromes		11
Genomic Imprinting/Anticipation: Fragile X Syndrome,		
Spinobulbar Muscular Atrophy, Myotonic Dystrophy		14
Indirect Analysis of Mutant Genes		15
Positional Cloning Prototype: Cystic Fibrosis		15
Neurofibromatosis		16
Direct Analysis of Mutant Genes		17
Detection of Point Mutations: α_1 -Antitrypsin Deficiency,		
McCune-Albright Syndrome, Vitamin D-Resistant Rickets.		17
Detection of Deletions: Isolated Growth Hormone		
Deficiency Type IA, Laron Dwarfism, 21-Hydroxylase		19
Deficiency		
Prenatal and Premorbid Diagnosis and Treatment of Disease.		20
21-Hydroxylase Deficiency		20
Multiple Endocrine Neoplasia Type 2A		21
Gene and Cancer Therapy		
Signal Transduction		
Gene Transfer—The Transgenic Animal		24
Cloning of Useful Proteins		25

Childhood Immunization Update. By Peter D. Reuman, Mobeen H. Rathore, and Elia M. Ayoub.		v	33
Newly Approved Vaccines			34
Haemophilus influenzae Conjugate Vaccines			34
Hepatitis B Virus Vaccine			36
Vaccines Under Trial			39
Acellular Pertussis Vaccine			39
Varicella Vaccine			41
Pneumococcal Vaccine			43
Hepatitis A Vaccine			44
Vaccines Under Development			45
Herpes Simplex Virus Vaccine.			45
Cytomegalovirus Vaccine			45
Respiratory Syncytial Virus Vaccines			46
Parainfluenza Vaccines			46
Rotavirus Vaccines			46
Streptococcal Vaccines			47
Mycoplasma Vaccine			49
Malaria Vaccine			49
Current Controversies			50
Poliovirus Vaccines			50
Measles Vaccine			51
Additional Guidelines to the Recommendations for	•	٠	01
Immunization			54
Routine Immunization			54
Children With Delayed or Unknown Immunization Status.			55
Children With Primary or Secondary Immune Deficiencies.			55
Travel			56
Legislative Issues			56
			00
Maternal Cocaine Use: Impact on Child Health and			
Development. By Deborah A. Frank, Karen Bresnahan, and Barry S.			
Zuckerman			65
Methodologic Issues			66
Identification of Exposure		•	66
Identification of Exposure	٠	٠	
Sample Selection Bias	٠	٠	70
Confounding Variables		٠	71
Lack of Blind Assessment and Comparison Populations Selection of Appropriate Outcome Measures		٠	71
* *		٠	
A Multifactorial Developmental Model			72
Primary vs. Secondary Effects			72
Transactional Model			72
Postnatal Influences			73

Cocaine	
Preliminary Data Regarding Effects on Fetal Neurotransmitters.	
Newborn Outcome	
Complications of Pregnancy	
Prematurity, Low Birth Weight, and Intrauterine Growth Retardation	. 76
The Role of Nutrition	
Structural Malformations	8.3
Neurologic Findings.	
Neonatal Neurobehavioral Correlates of Cocaine Exposure	
Findings After the Newborn Period	 82
Sudden Infant Death Syndrome	
Postneonatal Exposure to Cocaine	 82
Growth and Developmental Outcome After the Neonatal Period	. 84
	 . 04
Environmental Issues Contributing to Developmental	. 85
Outcome	
Social Disadvantage	
Addiction and Its Implications	 . 89
Recovery and Barriers to Recovery	
Implications for Public Policy and Clinical Care	
Cost of Maternal Cocaine Use	
Implications of Research Findings for Prenatal Intervention.	
Implications for Services to Children and Addicted Parents.	 . 92
Bone Marrow Transplantation.	101
By Richard Hong	
Biology of Bone Marrow Transplantation	 . 102
Histocompatibility Requirements	 . 102
Conditioning Requirements	 . 103
Chronology of Major Events During Bone Marrow	
Transplantation	
Unique Problems of Bone Marrow Transplantation	 . 105
Rejection	 . 105
Graft-vsHost Disease	 . 106
Veno-Occlusive Disease	 . 107
Secondary Malignancy	 . 108
Long-Term Effects of Conditioning Regimens	
Techniques	
T-Cell Depletion	109
Matched Unrelated Donors	

Confirmation of Engrattment and Search for Residual
Tumor
Results in Various Diseases
Malignancy
Immunodeficiency
Severe Aplastic Anemia
Fanconi's Anemia
Inborn Errors of Metabolism
Thalassemia
Future Prospects
Cytokines
In Utero Transplantation
Gene Therapy
Macrophage Targeting
Summary
The Current Status of Childhood Lead Toxicity. By Herbert L. Needleman
History
Studies of Asymptomatic Exposure
Long-Term Consequences of Early Exposure
Prenatal Exposure to Lead
Synthesis of Studies
How Does Lead Act?
What Is the Toxic Dose of Lead?
What Is the Extent of Excess Lead Exposure?
Why Has Progress in Lead Control Been Slow?
Advances in Therapy
Steps Toward Primary Prevention
Ending Childhood Lead Poisoning
The Follow-up of Infants Exposed to Chloride-Deficient
Formulas.
By Michael H. Malloy
History of Discovery of the Chloride-Deficient Formula 143
History of The Infant Formula Act
History of the National Institutes of Health Study
Development
Interim Follow-up Studies of Infants With Hypochloremic
Metabolic Alkalosis
Summary of Study Design and Results of School-Based

	Summary of Study Design and Results	of :	the	Н	M	Α					
	Follow-up Study										146
	Study Design and Result Critique										
	Public Interaction With Scientific Work .										
	Conclusions										157
Bo	ody Composition.										150
-	Kenneth J. Ellis and Buford L. Nichols, J										
	Two-Component Model of Body Composi										
	Multicompartmental Models of Body Com	-									
	Body Water Measurements										
	Body Potassium and Nitrogen Measureme										
	Total-Body Potassium										
	Total-Body Nitrogen										
	Bone Mineral Compartment										
	Body Fat Measurements										
	Changes in Body Composition With Grow	<i>r</i> th									176
By	eurologic Management. Stephen Ashwal, Ronald M. Perkin, Jose Inford Schneider, and Lawrence G. Tomas	ph si	<i>R</i> .	. T	ho	mį ·	osc	n,			185
	Epidemiology										186
	Clinical Presentation										186
	Laboratory Testing										187
	Pathophysiology										189
	Cerebral Metabolism										191
	Neuroimaging Studies										192
	Cerebral Blood Flow										194
	Cerebral Edema									,	197
	Cerebral Perfusion Pressure										200
	Autoregulation										
	Cerebral Blood Flow/Pco ₂ Reactivity										
	Treatment										
	General Approach to the Patient										
	Antimicrobial Therapy										205
	Treatment With Corticosteroids										206
	Management of Seizures										
	Fluid Management										
	An Approach to the Seriously III Patient										
	Conclusion										210

Rett Syndrome. By Christina M. Iyama	17
Clinical Presentation and Natural History	
The Infant	
The Toddler	
The Preschooler	19
The School Age Child	
The Adolescent and Adult	
Differential Diagnosis	
Clinical Variants	
Clinical Findings: Clues to Pathophysiology	25
Growth Retardation	
Seizures	26
Scoliosis and Orthopedic Complications	
Hyperventilation/Apnea	
Motor Disorders	
Vasomotor Disturbances	
Cognitive Function	
The Search for a Cause	
Genetics	
Treatment	
Family Stress	
Management of Menstruation	
Educational Programming and Therapy	
In Case of Death	
Conclusions and a Look to the Future	39
Transcatheter Closure of Cardiac Defects.	
By Michael J. Landzberg and James E. Lock	17
Patent Ductus Arteriosus	48
Secundum Atrial Septal Defects	
Ventricular Septal Defects	
Postoperative Residual Defects	
Vascular Embolizations	
Conclusions	
	00
Diuretic Treatment Agents. By Michael D. Bailie	73
Kidney Function During Development	73
Diuretic Pharmacology	76
	78

	Osmotic Diuretics	280
	Thiazide Diuretics and Related Drugs	
	Loop Diuretics	81
	Potassium-Sparing Diuretics	
	Diuretic Use in the III Premature and Newborn	
	Summary	84
N B	phrotic Syndrome in Childhood. Wm. Lane M. Robson and Alexander K.C. Leung 2	87
	Definitions	87
	Measurement of Proteinuria	
	Historical Highlights	
	Classification	
	Epidemiology	
	Genetic Aspects	
	Pathophysiology	192
	Proteinuria	92
	Edema	92
	Hyperlipidemia	93
	Immunopathogenesis	
	Clinical Manifestations	
	Primary Nephrotic Syndrome	
	Minimal-Lesion Nephrotic Syndrome	
	Secondary Nephrotic Syndrome	99
	Congenital	
	Laboratory Findings	
	Pathologic Findings	
	Complications	
	Renal Complications	
	Infection	
	Thromboemboli	03
	Failure to Thrive	
	Premature Atherosclerosis	
	Tetany	
	Differential Diagnosis	
	Management	
	Indications for Hospital Admission	06
	Diet	
	Diuretics and Albumin Infusion	06

Corticosteroids	. 307
Other Immunosuppressive Medications	. 308
Treatment of the Underlying Cause	. 310
Treatment of Congenital Nephrotic Syndrome	. 310
Miscellaneous	. 311
Renal Biopsy	. 311
Treatment of Relapses	. 311
Treatment of Complications	. 313
Education and Psychological Support of the Family	
Follow-up	
Prognosis	
Recurrence Risk in Transplanted Kidneys	
Summary	. 316
The Kidney in Systemic Disease: Part II—Autoimmune	
and Vascular Disorders.	
By Uri Alon, Bradley A. Warady, and Stanley Hellerstein	. 325
Primary Systemic Vasculitides	. 325
Classic Polyarteritis Nodosa	. 328
Microscopic Polyarteritis Nodosa	. 328
Overlap Syndrome	. 329
Wegener's Granulomatosis	. 330
Henoch-Schönlein Purpura	. 332
IgA Nephropathy	. 335
IgA Nephropathy and Henoch-Schönlein Purpura—Two	
Variants of the Same Disease?	. 338
Lupus Nephritis	. 339
Treatment	. 343
Summary	. 347
Renal Stones and Hypercalciuria.	
By Martin S. Polinsky, Bruce A. Kaiser, H. Jorge Baluarte, and	
Alan B. Gruskin	. 353
Pathophysiology of Urolithiasis	. 354
Etiology and Epidemiology	. 356
Clinical Disorders Associated With Urolithiasis.	
Calcium Stone Disease	
Uric Acid Stone Disease	. 363
Urolithiasis and Infection	. 364
Labour Comment Matabalian Associated With Change	
Disease	. 366
Congenital Urinary Tract Anomalies	. 368