## Contents

### SECTION I GENETICS AND EMBRYOLOGY, 1

1 Basic Genetic Principles, 1  
Fred Levine

2 Prenatal Diagnosis, 14  
Necta L. Vora | Barbara M. O'Brien

3 Basic Embryology, 23  
David L. Bolender | Stanley Kaplan

4 Regulation of Embryogenesis, 39  
Matthew K. Lee | David Warburton | Parviz Minoo

5 The Extracellular Matrix in Development, 49  
Sharareh Shojaie | Sandra Leibel | Martin Post

6 Stem Cell Biology, 54  
Evan Y. Snyder | Stephen Yip | Cameron Pernia | Colleen A. Lopez | Yang Liu | Eniko Sajti

7 Mechanisms of Cell Death in the Developing Brain, 76  
Claire Thornton | Henrik Hagberg

8 Angiogenesis, 85  
M. Luisa Iruela-Arispe | Ann Zovein

9 Epigenetics, 89  
William Schierding | Mark H. Vickers | Justin M. O'Sullivan | Wayne S. Cutfield

### SECTION II PLACENTA AND INTRAUTERINE ENVIRONMENT, 101

10 Placental Development, 101  
Hans-Georg Frank

11 Regulation of the Placental Circulation, 114  
Charles R. Rosenfeld

12 Mechanisms of Transfer Across the Human Placenta, 121  
Christina E. Hayward | Rebecca Lee Jones | Colin P. Sibley

13 Endocrine and Paracrine Function of the Human Placenta, 134  
Anna A. Penn

14 Fetal and Maternal Responses to Intraamniotic Infection, 144  
Roberto Romero | Piya Chaemsaiithong | Lami Yeo | Nikolina Docheva | Noppadol Chatyasit

### SECTION III DEVELOPMENTAL PHARMACOLOGY AND PHARMACOKINETICS, 187

15 Fetal Origins of Adult Disease: A Classic Hypothesis With New Relevance, 160  
Jed Friedman | Peter Russell Baker II

16 Physiologic Effects of Multiple Pregnancy on Mother and Fetus, 167  
Jennifer M.H. Amorosa | Jane Cleary-Goldman | Mary E. D'Alton

17 Placental Function in Intrauterine Growth Restriction, 176  
Yi-Yung Chen | Thomas Jansson

18 Basic Pharmacologic Principles, 187  
Vikrant K. Bhosle | Gabriel Altit | Julie Autmizguine | Sylvain Chemtob

19 Principles of Pharmacokinetics, 201  
Robert M. Ward | Steven E. Kern

20 Physicochemical and Structural Properties Regulating Placental Drug Transfer, 208  
Karel Allegaert | John N. Van Den Anker

21 Pharmacogenetics, 222  
Denis M. Grant

22 Drug Distribution in Fetal Life, 229  
Marianne Garland

23 Drug Transfer During Breast-Feeding, 239  
Thomas Hale | James Abbey

### SECTION IV INTRAUTERINE AND POSTNATAL GROWTH, 249

24 Circulatory and Metabolic Changes Accompanying Fetal Growth Restriction, 249  
Frederick Battaglia | Giacomo Meschia

25 Endocrine Factors Affecting Neonatal Growth, 256  
Yvonne K. Lee | Dennis M. Styne

26 Human Milk Composition and Function in the Infant, 273  
Donna Geddes | Foteini Hassiotou | Michael Wise | Peter Hartmann

27 Physiology of Lactation, 281  
James L. McManaman
SECTION V PERINATAL IRON, MINERAL, AND VITAMIN METABOLISM, 288

28 Fetal and Neonatal Iron Metabolism, 288
   Harry J. McArdle | Michael K. Georgiiff

29 Neonatal Calcium, Phosphorus, and Magnesium Homeostasis, 296
   Ran Namgung | Reginald C. Tsang

30 Zinc in the Fetus and Neonate, 313
   K. Michael Hambidge | Nancy F. Krebs

31 Vitamin A Metabolism in the Fetus and Neonate, 317
   A. Catharine Ross | Libo Tan | Sarah A. Owusu

32 Vitamin E Nutrition in the Fetus and Newborn, 326
   Jeffrey L. Segar | Edward F. Bell | Vinod K. Bhutani | Lois H. Johnson

33 Vitamin K Metabolism in the Fetus and Neonate, 336
   Martin J. Shearer

SECTION VI LIPID METABOLISM, 342

34 Maternal-Fetal Transfer of Lipid Metabolites, 342
   Emilio Herrera | Miguel Angel Lasunción

35 Brown Adipose Tissue: Development and Function, 354
   Jan Nedergraad | Barbara Cannon

36 Lipids as an Energy Source for the Premature and Term Neonate, 364
   Emilio Herrera | Henar Ortega-Senovilla

37 Ketone Body Metabolism in the Neonate, 370
   Baris Ercal | Peter A. Crawford

38 Long-Chain Polyunsaturated Fatty Acids in the Developing Central Nervous System, 380
   Susan E. Carson | Carol L. Cheatham | John Colombo

SECTION VII CARBOHYDRATE METABOLISM, 390

39 Metabolism of Glucose and Methods of Investigation in the Fetus and Newborn, 390
   Satish C. Kalhan

40 Carbohydrate Metabolism During Pregnancy, 404
   Alison Chu | Sherin U. Devaskar

41 Oxygen Consumption and General Carbohydrate Metabolism of the Fetus, 405
   Anthony F. Philippis

42 Role of Glucoregulatory Hormones in Hepatic Glucose Metabolism During the Perinatal Period, 418
   Richard M. Cowett

43 Cell Glucose Transport and Glucose Handling During Fetal and Neonatal Development, 428
   Rebecca A. Simmons

SECTION VIII PROTEIN METABOLISM, 436

44 General Concepts of Protein Metabolism, 436
   Johannes (Hans) B. van Goudoever | Dwight E. Matthews

45 Fetal Requirements and Placental Transfer of Nitrogenous Compounds, 444
   Laura Davidson Brown | Timothy R.H. Regnault | William W. Hay, Jr.

SECTION IX THERMOREGULATION, 459

46 Temperature Control in Newborn Infants, 459
   Rakesh Sahni

47 Responses of the Fetus and Neonate to Hypothermia, 482
   Alistair Jan Gunn | Laura Bennet

SECTION X SKIN, 490

48 Structure and Development of the Skin and Cutaneous Appendages, 490
   David H. Chu | Cynthia A. Loomis

49 Physiologic Development of the Skin, 498
   Steven B. Hoath | Kara N. Shah

SECTION XI FETAL AND NEONATAL CARDIOVASCULAR PHYSIOLOGY, 515

50 Cardiovascular Development, 515
   Brian S. Snarr | Tim C. McQuinn | Andy Wessels

51 Developmental Electrophysiology in the Fetus and Neonate, 522
   Janette F. Strasburger | Annette Wacker-Guermann
<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Pages</th>
<th>Authors/Contributors</th>
</tr>
</thead>
<tbody>
<tr>
<td>52</td>
<td>Developmental Biology of the Pulmonary Vasculature</td>
<td>539</td>
<td>Marlene Rabinovitch</td>
</tr>
<tr>
<td>53</td>
<td>Development of the Gastrointestinal Circulation in the Fetus and Newborn</td>
<td>555</td>
<td>Upender K. Munshi, David A. Clark</td>
</tr>
<tr>
<td>54</td>
<td>Physiology of Congenital Heart Disease in the Neonate</td>
<td>560</td>
<td>Thomas J. Kulik</td>
</tr>
<tr>
<td>55</td>
<td>Neural Regulation of Blood Pressure During Fetal and Newborn Life</td>
<td>573</td>
<td>Jeffrey L. Segar, Dino A. Giussani</td>
</tr>
<tr>
<td>56</td>
<td>Developmental Effects on the Fetal Circulation</td>
<td>584</td>
<td>Lucy R. Green, Mark A. Hanson</td>
</tr>
<tr>
<td>57</td>
<td>Mechanisms Regulating Closure of the Ductus Arteriosus</td>
<td>592</td>
<td>Ronald I. Clyman</td>
</tr>
<tr>
<td>58</td>
<td>Umbilical Circulation</td>
<td>599</td>
<td>Torvid Kiscrued, Gutorm Haugen</td>
</tr>
<tr>
<td>59</td>
<td>Fetal and Placental Circulation During Labor</td>
<td>611</td>
<td>Karel Maršál</td>
</tr>
<tr>
<td>60</td>
<td>Physiology of Resuscitation</td>
<td>619</td>
<td>Ola Didrik Saugstad</td>
</tr>
<tr>
<td>61</td>
<td>Normal and Abnormal Structural Development of the Lung</td>
<td>627</td>
<td>Susan E. Wert</td>
</tr>
<tr>
<td>62</td>
<td>Regulation of Alveolarization</td>
<td>642</td>
<td>Christophe Delacourt, Alice Hadchouel</td>
</tr>
<tr>
<td>63</td>
<td>Physiologic Mechanisms of Normal and Altered Lung Growth Before and After Birth</td>
<td>646</td>
<td>Megan J. Wallace, Stuart B. Hooper, Richard Harding</td>
</tr>
<tr>
<td>64</td>
<td>Molecular Mechanisms of Lung Development and Lung Branching Morphogenesis</td>
<td>658</td>
<td>Sharareh Shojaie, Martin Post</td>
</tr>
<tr>
<td>65</td>
<td>Regulation of Liquid Secretion and Absorption by the Fetal and Neonatal Lung</td>
<td>667</td>
<td>David P. Carlton</td>
</tr>
<tr>
<td>66</td>
<td>Upper Airway Structure: Function, Regulation, and Development</td>
<td>676</td>
<td>Thomas H. Shaffer, Raymond B. Penn, Maria R. Wolfson</td>
</tr>
<tr>
<td>67</td>
<td>Regulation of Lower Airway Function</td>
<td>685</td>
<td>Richard J. Martin, Thomas M. Raffay, Arji Faksh, Y.S. Prakash</td>
</tr>
<tr>
<td>68</td>
<td>Functional Development of Respiratory Muscles</td>
<td>692</td>
<td>Carlos B. Mantilla, Mohamed A. Fahim, Joline E. Brandenburg, Gary C. Sieck</td>
</tr>
<tr>
<td>69</td>
<td>Mechanics of Breathing</td>
<td>706</td>
<td>Jacopo P. Mortola</td>
</tr>
<tr>
<td>70</td>
<td>Pulmonary Gas Exchange in the Developing Lung</td>
<td>714</td>
<td>William E. Truog, John P. Kingsella</td>
</tr>
<tr>
<td>71</td>
<td>Oxygen Transport and Delivery</td>
<td>724</td>
<td>Patrick J. McNamara, Alif El-Khuffash</td>
</tr>
<tr>
<td>72</td>
<td>Control of Breathing in Fetal Life and Onset and Control of Breathing in the Neonate</td>
<td>737</td>
<td>Ruben E. Alvaro, Henrique Rigatto</td>
</tr>
<tr>
<td>73</td>
<td>Basic Mechanisms of Oxygen Sensing and Response to Hypoxia</td>
<td>748</td>
<td>Dan Zhou, Gabriel G. Haddad</td>
</tr>
<tr>
<td>74</td>
<td>Evaluation of Pulmonary Function in the Neonate</td>
<td>754</td>
<td>Emidio M. Sivieri, Kevin Dysart, Soraya Abbasi</td>
</tr>
<tr>
<td>76</td>
<td>Impaired Lung Growth After Injury in Premature Lung</td>
<td>771</td>
<td>Kurt H. Albertine, Theodore J. Pysher, Bradley A. Yoder</td>
</tr>
<tr>
<td>77</td>
<td>Antenatal Factors That Influence Postnatal Lung Development and Injury</td>
<td>778</td>
<td>Suhas G. Kallapur, Alan H. Jobe</td>
</tr>
<tr>
<td>78</td>
<td>Regulation of Pulmonary Circulation</td>
<td>786</td>
<td>Yuansheng Gao, J. Usha Raj</td>
</tr>
<tr>
<td>79</td>
<td>Historical Perspective</td>
<td>795</td>
<td>John A. Clements</td>
</tr>
<tr>
<td>80</td>
<td>Surfactant Homeostasis: Composition and Function of Pulmonary Surfactant Lipids and Proteins</td>
<td>798</td>
<td>Jeffrey A. Whitsett</td>
</tr>
<tr>
<td>81</td>
<td>Structure and Development of Alveolar Epithelial Cells</td>
<td>809</td>
<td>Henry J. Rozycki, Karen D. Hendricks-Muñoz</td>
</tr>
<tr>
<td>82</td>
<td>Regulation of Surfactant-Associated Phospholipid Synthesis and Secretion</td>
<td>813</td>
<td>Wolfgang Bernhard</td>
</tr>
<tr>
<td>83</td>
<td>Antenatal Hormonal Therapy for Prevention of Respiratory Distress Syndrome</td>
<td>825</td>
<td>Ian Gross, Philip L. Ballard</td>
</tr>
<tr>
<td>84</td>
<td>Surfactant Treatment</td>
<td>831</td>
<td>Alan H. Jobe, Suhas G. Kallapur</td>
</tr>
</tbody>
</table>
SECTION XIV PHYSIOLOGY OF GASTROINTESTINAL TRACT IN THE FETUS AND NEONATE, 855

86 Trophic Factors and Regulation of Gastrointestinal Tract and Liver Development, 855
Douglas G. Burris

87 Organogenesis of the Gastrointestinal Tract, 861
Maxime M. Mabe | Michael A. Helmuth | Noah F. Shroyer

88 Development of the Enteric Nervous System, 870
Delma L. Broussard | Steven M. Altschuler

89 Development of Gastric Secretory Function, 876
Joshua D. Prozialeck | Barry K. Wershil

90 Development of Gastrointestinal Motility, 881
Kara Gross Margolis | Joseph A. Picoraro

91 Development of the Exocrine Pancreas, 888
Lori Sussel

92 Digestive-Absorption Functions in Fetuses, Infants, and Children, 897
Josef Neu

93 The Developing Microbiome of the Fetus and Newborn, 905
Josef Neu

SECTION XV LIVER AND BILIRUBIN METABOLISM, 909

94 Organogenesis and Histologic Development of the Liver, 909
Steven Lobritto

95 Bile Acid Metabolism During Development, 913
Heidi Eigenrauch Karpen | Saul J. Karpen

96 Neonatal Bilirubin Metabolism, 929
William J. Cashore

97 Hereditary Contribution to Neonatal Hyperbilirubinemia, 933
Michael Kaplan | Cathy Hammerman

98 Mechanistic Aspects of Phototherapy for Neonatal Hyperbilirubinemia, 942
Vinod K. Bhutani | Angelo A. Lamola

SECTION XVI THE KIDNEY, 953

99 Development of the Kidney: Morphology and Mechanisms, 953
Ian M. Smyth | Luise A. Cullen-McEwen | Georgina Caruana | M. Jane Black | John F. Bertram

100 Functional Development of the Kidney in Utero, 965
Douglas G. Matisell | Michael J. Hitt

101 Development and Regulation of Renal Blood Flow in the Neonate, 977
Michael J. Solhaug | Pedro A. Jose

102 Development of the Renin-Angiotensin System, 983
Francine G. Smith

103 Postnatal Development of Glomerular Filtration Rate in Neonates, 993
Jean-Pierre Guignard

104 Renal Transport of Sodium During Development, 1002
Michel Baum

105 Potassium Homeostasis in the Fetus and Neonate, 1011
Matthias T. Wolf | Corinne Benchimol | Lisa M. Satlin | Raymond Quigley

106 Role of the Kidney in Calcium and Phosphorus Homeostasis, 1024
Abhijet Pal | Frederick J. Kaskel

107 Transport of Amino Acids in the Fetus and Neonate, 1034
Raymond Quigley

108 Organic Anion Transport in the Developing Kidney, 1040
Sun-Young Ahn | Sanjay K. Nigam

109 Concentration and Dilution of Urine, 1046
Silvia Iacobelli | Jean-Pierre Guignard

110 Urinary Acidification, 1066
Alice M. Wang | George J. Schwartz | Seth L. Alper

111 Response to Nephron Loss in Early Development, 1074
Jennifer R. Charlton | Robert L. Chevalier

SECTION XVII FLUID AND ELECTROLYTE METABOLISM, 1081

112 Fluid Distribution in the Fetus and Neonate, 1081
Chang-Ryu Kim | Anup C. Katheria | Judith S. Mercer | Barbara S. Stonestreet
SECTION XVIII DEVELOPMENTAL HEMATOPOIESIS, 1094

114 Developmental Biology of Stem Cells: From the Embryo to the Adult, 1094
Momoko Yoshimoto | Mervin C. Yoder

115 Developmental Granulocytopenia, 1104
Akhil Maheshwari | Robert D. Christensen

116 Developmental Erythropoiesis, 1112
Robin K. Ohls

117 Developmental Megakaryocytopenia, 1135
Martha Sola-Visner | Haley Ramsey

SECTION XIX HEMOSTASIS, 1151

118 Developmental Hemostasis, 1151
Paul Monagle

119 Platelet-Vessel Wall Interactions, 1158
Thomas G. Diacovo

SECTION XX DEVELOPMENTAL IMMUNOBIOLOGY, 1163

120 Host Defense Mechanisms Against Bacteria, 1163
Tobias R. Kollmann | Arnaud Marchant

121 Host Defense Mechanisms Against Fungi, 1171
Melinda Erdös | László Maródi | Richard B. Johnston, Jr.

122 Host Defense Mechanisms Against Viruses, 1175
James E. Crowe, Jr.

123 T Cell Development, 1198
Melinda Erdös | Beáta Tóth | László Maródi

124 B Cell Development, 1202
Tucker W. LeBien

125 Mononuclear Phagocyte System, 1208
Pascal M. Lavoie | Ofer Levy

126 Normal and Abnormal Neutrophil Physiology in the Newborn, 1216
Joyce M. Koenig | Joseph M. Bliss | M. Michele Mariscalco

127 The Complement System of the Fetus and Newborn, 1230
Melvin Berger

SECTION XXI NEUROLOGY, 1294

131 Development of the Nervous System, 1294
Christopher J. Yuskaitis | Scott L. Pomeroy

132 Development of the Blood-Brain Barrier, 1314
Jérôme Badaut | Susan S. Cohen | Daniela Virgintino | Barbara S. Stonestreet

133 Trophic Factor, Nutritional, and Hormonal Regulation of Brain Development, 1326
Jeanette R. Pleasure | David Pleasure | Samuel J. Pleasure

134 Intraventricular Hemorrhage in the Neonate, 1333
Brian H. Walsh | Terrie E. Inder | Joseph J. Volpe

135 Cerebellar Development—The Impact of Preterm Birth and Comorbidities, 1350
Emily W.Y. Tam | Manon J.N.R. Benders | Vivi M. Heine

136 Electroencephalography in the Preterm and Term Infant, 1362
Maria Roberta Cilio | Francesco Pisani

137 Developmental Aspects of Pain, 1390
Manon Ranger | Simon Beggs | Ruth E. Grunau

SECTION XXII SPECIAL SENSORY SYSTEMS IN THE FETUS AND NEONATE, 1396

138 Early Development of the Human Auditory System, 1396
Kelsey L. Anbuhl | Kristin M. Uhler | Lynne A. Werner | Daniel J. Tollin

139 Development of Olfaction and Taste in the Human Fetus and Neonate, 1411
Harvey B. Sarnat

SECTION XXIII ORTHOPEDICS, 1421

140 The Growth Plate: Embryologic Origin, Structure, and Function, 1421
Emmanuel Grigoriou | Ashley Trocle | John P. Dormans
141 Ontogenesis of Striated Muscle, 1430
Harvey B. Samat

SECTION XXIV ENDOCRINE FUNCTION, 1451

142 Hypothalamus: Neuroendometabolic Center, 1451
Adda Grimberg | Jessica Katz Kutzikov

143 Growth Factor Regulation of Fetal Growth, 1461
Colin P. Hawkes | Lorraine E. Levitt Katz

144 Growth Hormone, Prolactin, and Placental Lactogen in the Fetus and Newborn, 1470
Nursem Gurunca | Mark A. Sperling

145 Luteinizing Hormone and Follicle-Stimulating Hormone Secretion in the Fetus and Newborn Infant, 1476
Sumana Narasimhan | Ethel G. Clemente | Neha V. Vyas

146 Development of the Corticotropin-Releasing Hormone–Corticotropin System in the Mammalian Fetus, 1488
Jeffrey Schwartz | James C. Rose

147 Fetal and Neonatal Adrenocortical Physiology, 1494
Kristi L. Watterberg | Louis J. Muglia

148 Fetal and Neonatal Thyroid Physiology, 1503
Stephen A. Huang

SECTION XXV OVARY AND TESTIS, 1510

149 Genetics of Sex Determination and Differentiation, 1510
Peter James Ellis | Robert P. Erickson

150 Differentiation of the Ovary, 1520
Claus Yding Andersen | Andrew J. Childs | Richard A. Anderson

151 Testicular Development and Descent, 1528
Mary M. Lee

SECTION XXVI PATHOPHYSIOLOGY OF NEONATAL DISEASES, 1536

152 Pathophysiology of Neonatal Sepsis, 1536
James L. Wynn | Hector R. Wong

153 Pathophysiology of Neonatal Hypoglycemia, 1552
Colin P. Hawkes | Charles A. Stanley

154 Pathophysiology of Cardiomyopathies, 1563
Jeffrey A. Towbin | John Lynn Jeffries | Thomas D. Ryan

155 Pathophysiology of Persistent Pulmonary Hypertension of the Newborn, 1576
Satyan Lakshmimurugan | Robin H. Steinhorn

156 Pathophysiology of Shock in the Fetus and Neonate, 1588
Shahab Noori | Philippe S. Friedlich | Istvan Seri

157 Pathophysiology of Apnea of Prematurity, 1595
Richard J. Martin

158 Pathophysiology of Respiratory Distress Syndrome, 1604
Alan H. Jobe

159 Pathophysiology of Meconium Aspiration Syndrome, 1619
Jason Gien | John P. Kinsella

160 Pathophysiology of Bronchopulmonary Dysplasia, 1625
Eduardo H. Bancelari | Deepak Jain

161 Pathophysiology of Ventilator-Dependent Infants, 1632
Howard B. Panitch

162 Pathophysiology of Gastroesophageal Reflux, 1643
Sudarshan R. Jadcherla

163 Pathophysiology of Neonatal Necrotizing Enterocolitis, 1652
Michael Caplan

164 Pathophysiology of Kernicterus, 1657
Thor Willy Ruud Hansen

165 Pathophysiology of Neonatal Acute Kidney Injury, 1668
Jennifer G. Jetton | David T. Selewski | Jennifer R. Charlton | David J. Askenazi

166 Pathophysiology of Edema, 1676
David P. Carlton

167 Pathophysiology of Retinopathy of Prematurity, 1681
Efrén González | Andreas Stahl | Ann Hellström | Lois E.H. Smith

168 Pathophysiology of Hypoxic-Ischemic Brain Injury, 1686
Patrick S. McQuillen | Susan J. Vannucci | Henrik Hagberg

169 Pathophysiology of Neonatal White Matter Injury, 1695
Steven P. Miller | Stephen A. Back
170 Pathophysiology of Neonatal Bacterial Meningitis, 1703
Tatiana Barichello

171 Pathophysiology of Neural Tube Defects, 1712
Enrico Danzer | Natalie E. Rintoul | N. Scott Adzick

172 Pathophysiology of Preeclampsia, 1724
Sarosh Rana | S. Ananth Karumanchi

173 Pathophysiology of Preterm Birth, 1732
Shirin Khanjani | David A. MacIntyre | Phillip R. Bennett

174 Pathophysiology of Chorioamnionitis: Host Immunity and Microbial Virulence, 1737
Tara Marie Randis | Adam J. Ratner