

# Contents

## Part I Discovery and Origins

<b>1</b>	<b>Discovery</b> .....	3
	Zwischenstrang .....	5
	A Brief Overview of the Past 120 Years .....	6
	1890–1950s .....	6
	1960s–1970s .....	9
	1980s to the 21st Century .....	9
	Neural Crest and Germ-Layer Theory .....	12
	Germ-Layer Theory .....	14
	Multiple Tissues from Single Layers .....	15
	Heads and Tails .....	16
	Secondary Neurulation and Tail Buds .....	17
	Induction of Tail Buds .....	18
	Neural Crest as the Fourth Germ Layer .....	19
	Neural Crest as Inhibitor .....	20
	Notes .....	21
<b>2</b>	<b>Embryological Origins and the Identification of Neural Crest Cells</b> ..	23
	Neural Crest .....	23
	Before Neurulation .....	23
	Establishing the Epidermal–Neural Border .....	25
	NCC Markers and Specification of the NC .....	27
	HNK-1 and <i>Pax7</i> .....	28
	<i>Snail-2</i> , <i>Bmp4</i> , and Cadherins .....	29
	Sox Genes .....	31
	Wnt genes .....	34
	Specification of Ectoderm as Neural or Epidermal .....	38
	NC Induction .....	39
	Bmps, Wnts, and Fgfs .....	39
	<i>Xenopus</i> .....	40

Chicken Embryos . . . . .	42
A Role for Notch in NCC Induction . . . . .	42
A Role for Bmps in NCC Induction and Beyond . . . . .	46
Zic3 and Zic5 . . . . .	47
Msx Genes and Specification of NCCs . . . . .	49
Establishing Cranial and Trunk Neural Crest . . . . .	51
Chicken Embryos . . . . .	52
Mouse Embryos . . . . .	53
Ectoderm from the Most Rostral Neural Tube . . . . .	53
Rostrocaudal Patterning of CNC . . . . .	54
Hox Genes . . . . .	54
A Role for Mesoderm . . . . .	56
The Midbrain–Hindbrain Boundary . . . . .	57
Dlx Genes and Dorsovenral Patterning of CNC . . . . .	58
Notes . . . . .	58
<b>3 Delamination, Migration, and Potential . . . . .</b>	<b>63</b>
Delamination . . . . .	63
Cellular Changes Driving Delamination . . . . .	66
Cadherins . . . . .	68
Extracellular Spaces and Delamination . . . . .	70
Migration . . . . .	71
Pathways of CNCC Migration . . . . .	71
Pathways of TNCC Migration . . . . .	73
Migration into Dorsal Fins and Tails . . . . .	76
Molecular Control of NCC Migration . . . . .	78
Extracellular Matrices, Cell Surface Ligands, and Receptors . . . . .	78
Permitting Migration . . . . .	79
Fibronectin . . . . .	80
Proteoglycan Complexes . . . . .	81
Neural Crest Cells Contribute to Extracellular Matrices to Permit Migration . . . . .	82
Thrombospondins . . . . .	82
Tyrosine Kinases Receptors (Trk) . . . . .	84
Ephrins and Eph Receptors . . . . .	84
Inhibiting Migration . . . . .	84
Components of ECMs . . . . .	84
Guiding Migrating NCCs . . . . .	85
Barriers and Components of ECMs . . . . .	85
The Environment at the Final Destination . . . . .	86
Endothelins . . . . .	89
Semaphorins, Delamination, and Migration . . . . .	90
Subpopulations of NCCs . . . . .	92
Restricted Premigratory and Early Migrating Populations of TNCCs . . . . .	94

Restriction During Migration . . . . .	97
Restriction Along the Neural Axis . . . . .	97
Differentiation . . . . .	99
Differentiation of Bipotential Cells . . . . .	110
A Role for Growth Factors . . . . .	110
Dedifferentiate and Redifferentiate . . . . .	111
Summary . . . . .	112
Notes . . . . .	113
<b>4 Evolutionary Origins . . . . .</b>	<b>117</b>
Precursors of the Neural Crest . . . . .	118
Cephalochordates . . . . .	122
Genes and Gene Networks in Cephalochordates . . . . .	125
AmphiSnail1 . . . . .	126
Hox genes: <i>AmphiHox1–AmphiHox12</i> . . . . .	127
AmphiDll . . . . .	128
AmphiOtx . . . . .	129
AmphiBmp . . . . .	130
AmphiPax . . . . .	130
Retinoic Acid and Retinoic Acid Receptors . . . . .	131
Urochordates–Ascidians . . . . .	134
Nervous System and Notochord . . . . .	135
Pigment Cells . . . . .	136
Calcitonin . . . . .	136
Bipotentiality and Conditional Specification . . . . .	137
Genetic Control of Ascidian Neural Development . . . . .	137
Bmps . . . . .	138
Snail and Hnf3 . . . . .	138
Pax Genes . . . . .	138
Fossil Chordates . . . . .	139
Burgess Shale . . . . .	139
Chengjiang Formation . . . . .	140
The First Vertebrates . . . . .	141
The Pharyngeal Skeleton . . . . .	141
The Origin of Cartilage . . . . .	142
Comparative Genomics and Bioinformatics . . . . .	146
Molecular Fingerprinting: Genetic Labeling/Selection and GeneChip Microarray Technology . . . . .	149
Jawless Vertebrates and the Origin of Jaws . . . . .	149
Jaws from Gill Arches? . . . . .	150
Notes . . . . .	153
<b>Part II Neural-Crest Derivatives</b>	
<b>5 Pigment Cells (Chromatophores) . . . . .</b>	<b>159</b>
Types of Chromatophores . . . . .	160

Melanosomes . . . . .	162
Lampreys . . . . .	163
Urodele and Anuran Amphibians . . . . .	163
Patterns of Pigmentation . . . . .	164
Larval-to-Adult Patterns . . . . .	165
Teleost Fish . . . . .	167
Migration and Cell Fate . . . . .	168
Larval Patterns . . . . .	169
Genes and Cell Lines . . . . .	170
Birds . . . . .	172
Patterning Feather Tracts . . . . .	173
Non-Avian Reptiles . . . . .	173
Mammals . . . . .	174
Pattern Formation . . . . .	174
Neurocristopathies . . . . .	175
Notes . . . . .	176
<b>6 Neuronal Cells and Nervous Systems . . . . .</b>	<b>179</b>
The Neural Crest, Neurons, and Nervous Systems . . . . .	180
The Peripheral Nervous System—Spinal and Cranial Ganglia . . . . .	181
Placodal Ectoderm . . . . .	183
Placodal Markers and Specification of Placodal Ectoderm . . . . .	189
The Panplacodal Domain . . . . .	191
Induction of Individual Placodes . . . . .	192
The Autonomic Nervous System . . . . .	193
Schwann Cells . . . . .	195
Glial Cells . . . . .	195
Vagal and Sacral Neural Crest . . . . .	197
Rohon–Béard Neurons . . . . .	197
Apoptosis Removes R–B Neurons . . . . .	198
Neural Crest Origin and Relationships to Other Neurons . . . . .	198
Genetic Control of R–B Neurons . . . . .	199
Notes . . . . .	200
<b>7 Cartilage Cells and Skeletal Systems . . . . .</b>	<b>203</b>
Pharyngeal Skeletons of Hagfish . . . . .	205
Pharyngeal Skeletons of Lamprey . . . . .	208
Cartilages . . . . .	208
Vitamin A . . . . .	213
Amphibian Craniofacial Skeletons . . . . .	213
Extirpating and Transplanting Amphibian Neural Crest . . . . .	214
Epithelial–Mesenchymal Interaction Required to Initiate Chondrogenesis . . . . .	217
Cascades of Interactions in Amphibian Craniofacial Development . . . . .	218
Labeling Amphibian CNCCs . . . . .	221
Timing of Migration . . . . .	223

Mapping CNCCs in Fish . . . . . 227  
     Elasmobranchs . . . . . 227  
     Teleosts . . . . . 228  
 Zebrafish Mutants and Pharyngeal Arch Development . . . . . 228  
     Distalless (*Dlx*) and the First and Second Pharyngeal Arches . . . . . 228  
     Chameleon (*Con*) and the Caudal Pharyngeal Arches . . . . . 229  
     Chinless (*Chn*) and the Absence of NCC from all Pharyngeal Arches . 229  
     Ninja and the Growth of Pharyngeal Arch Cartilages . . . . . 229  
 Skeletogenic NCCs in Reptiles . . . . . 230  
     CNCCs . . . . . 230  
     TNCCs . . . . . 231  
 Avian CNCCs . . . . . 231  
     <sup>3</sup>H-thymidine Labeling . . . . . 231  
     Quail/Chicken Chimeras . . . . . 232  
     The Chondrogenic CNC . . . . . 232  
     Cell Lineages in CNCCs . . . . . 233  
     CNCCs and Muscle Patterns . . . . . 237  
 Mapping the Mouse CNC . . . . . 238  
 Notes . . . . . 244

**8 Teeth and Hearts: The Odontogenic and Cardiac Neural Crests . . . . 247**  
 Teeth . . . . . 247  
     The Odontogenic Neural Crest . . . . . 248  
     Teeth but not Cartilage from Trunk NCCs . . . . . 250  
     Cartilage from TNCCs? . . . . . 252  
     Origination of Dentine and Bone . . . . . 253  
 Hearts . . . . . 255  
     Indirect Effects of Cranial NCCs on Heart Function . . . . . 256  
     Direct Effects of Cranial NCCs on Heart Function . . . . . 256  
     The Avian Cardiac Neural Crest . . . . . 257  
     Cardiac Cartilages . . . . . 260  
     Cardiac Neural Crest in Fish and Amphibians . . . . . 261  
     Cardiac Neural Crest in Mammals . . . . . 261  
     Cardiac Defects . . . . . 262  
 Notes . . . . . 264

**Part III Abnormal Development and the Neural Crest**

**9 Neurocristopathies . . . . . 269**  
 Antiquity . . . . . 269  
 Syndromology and Neural Tube Defects . . . . . 269  
 The Utility of the Germ-Layer Theory . . . . . 271  
 Types of Neurocristopathies . . . . . 273  
 CHARGE Syndrome . . . . . 276

PAX6 and CHD7 . . . . .	276
Neuroblastomas . . . . .	278
The Neoplastic State . . . . .	278
Diagnosis . . . . .	279
RaLP . . . . .	279
Model Systems . . . . .	280
von Recklinghausen Neurofibromatosis . . . . .	280
Involvement of Non-Neural-Crest Cells . . . . .	282
John Merrick—the ‘Elephant Man’ . . . . .	282
Animal Models and Mutations . . . . .	283
APUDomas . . . . .	284
Hirschsprung Disease . . . . .	286
DiGeorge Syndrome . . . . .	288
Genetics . . . . .	289
Genes Involved . . . . .	289
Notes . . . . .	291
<b>10 NCC Development Revisited in the Context of Birth Defects . . . . .</b>	<b>295</b>
Susceptible Stages of Neural Crest Development . . . . .	298
Defective Migration . . . . .	299
Defective Proliferation . . . . .	300
Enhanced Cell Death . . . . .	300
Defective Induction . . . . .	301
Vitamin A, Craniofacial Defects, and the Neural Crest . . . . .	302
Direct Action In Vivo . . . . .	302
Craniofacial Defects . . . . .	305
Mechanisms of Action . . . . .	308
Indirect Effects . . . . .	309
Evolutionary Origins of Sensitivity to Retinoic Acid . . . . .	309
Defects Following Disruption of the <i>Hox</i> Code . . . . .	310
Hoxa1 . . . . .	310
Hoxa2 . . . . .	311
Hoxa1, Hoxa2, and Hoxb1 . . . . .	311
Mutations and Birth Defects . . . . .	312
Looptail . . . . .	312
Spotch . . . . .	312
Regulation . . . . .	314
Sources of Cells . . . . .	316
Completeness of Regulation . . . . .	316
Pharyngeal-Arch Regulation . . . . .	317
Dorsal Root Ganglion Regulation . . . . .	317
Regulation of Cardiac Neural Crest . . . . .	319
Placodal Regulation from the Cardiac Neural Crest? . . . . .	320
Neural Crest Cells as Stem Cells . . . . .	321
Bi-, Tri-, and Multipotential NCCs . . . . .	321

What is a Stem Cell? ..... 322  
NCCs as Stem Cells ..... 323  
Notes ..... 325

**Common Names of Species Discussed ..... 329**

**Species (with Common Names) Arranged by Major Groups ..... 333**

**References ..... 339**

**Index ..... 387**